Factors Associated With Survival of Patients on Dialysis

Fathi Abdalla Lajili

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In the name of God the Beneficent, the Merciful بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Dedication

To

My father for being the rock of support and showing me the importance of education

My mother for her prayers, for being the loving soul and for making everything worthwhile

My wife, my friend, my love of my life (Huda Elkadar), for her devotion, patience and constant encouragement throughout the time we spent in Edinburgh.

Also dedicated to my brothers and sisters for their continues support

Every body might say this about their beloved ones, but I can not imagine a person having better Family than mine.

Declaration

I, Fathi Lajili hereby declare that I am the author of this work. The work of this thesis is a record has been done by myself and has not previously been accepted for a higher degree. This work has been carried out under the supervision of Professor Neil Turner.

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Abstract

Dialysis patients have higher rates of mortality than the normal population. The increased mortality among dialysis patients is associated with age, presence of comorbid conditions on starting dialysis, and poor nutritional status indicated by several nutritional markers and inflammation. This project sought to analyse these issues in a closely studied cohort of patients in South East Scotland.

In the first study subjective global assessment (SGA) of nutritional status was interrogated as a possible independent risk factor for 122 prevalent dialysis patients. The results showed age, comorbidity, SGA and C-reactive protein were associated with patient survival, and that significant additional information was provided by measuring SGA. In the second study factors associated with survival were examined in 183 consecutive patients starting renal replacement therapy in South East Scotland in 2003 and 2004. The results revealed that age, comorbidity, initial access and serum cholesterol all affected patients survival. In the Third study this 2003 and 2004 cohort was compared with a similar cohort commencing dialysis between 1997 and 2000 in South East Scotland. The results showed that median age rose from 63 to 65 and comorbidity increased but 2 year survival rate was unchanged and there was a substantial reduction in hospitalisation. The reason for improvement can not be identified with certainty but it could be because: between the two studies the unit moved hospitals and gained more nephrologists; additional machines were introduced, using high flux dialysers and more rigorous audit was implemented particularly in the haemodialysis services.

Publications

Abstracts

- **Lajili FA,** Turner AN, Metcalfe W, Elliot H, Robb L: Subjective Global Assessment (SGA) and Survival Advantages in Dialysis Patients. Scottish Renal Association meeting 2007 November 17, Dumfries
- **Lajili FA,** Turner AN, Metcalfe W: Factors Associated with Survival of patients on dialysis. Scottish Renal Association meeting 2007 November 17, Dumfries.
- **Lajili FA**, Turner AN, Metcalfe W, Elliot H, Robb L: Subjective Global Assessment (SGA) and Survival Advantages in Dialysis Patients. The 6th Libyan and the 3rd Maghrebian congress of nephrology and renal transplantation the 1st Maghrebian transplant games 2008 February 24 Tripoli-Libya.
- **Lajili FA,** Turner AN, Metcalfe W: Studies of Survival on Dialysis in South East Scotland. BRS/RA Annual conference 2008 May 16, Glasgow.

Papers in preparation

- Lajili FA, Turner AN, Metcalfe W. Improved outcomes for high risk dialysis patient in South East Scotland
- Lajili FA, Turner AN, Metcalfe W, Elliot H, Robb L. Subjective Global Assessment is an independent predictor of survival in dialysis patients.
- Lajili FA, Turner AN, Metcalfe: Review of outcomes of 2003 and 2004 dialysis in South East Scotland and compared with similar cohort commencing dialysis in between 1997 and 2000. Edren.org.

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Abbreviations

Arteriovenous Fistula	AVF
Arteriovenous Graft	AVG
Australia and New Zealand Dialysis and Transplant Registry database	ANZDATA
Body Mass Index	BMI
Canada and United States of America Study	CANUSA
Cardiovascular Disease	CVD
Central Venous Catheter	CVC
Cerebrovascular disease	CeVD
Charlson Comorbidity index	CCI
Chronic Kidney Disease	CKD
Chronic Pulmonary Disease	CPD
Congestive Cardiac Failure	CCF
Connective Tissue Disease	CT-disease
C-reactive Protein	CRP
Data from Dialysis Outcome and Practice Pattern Study	DOPPS
Diabetes Mellitus	DM
Disease Outcomes Quality Initiative	DOQI
End Stage Renal Disease	ESRD
Estimated Glomerular Filtration Rate	eGFR
European Renal Association-European Dialysis and Transplant Association	ERA-EDTA
Glomerulonephritis	GN
Health Related Quality of Life	HRQoL
Interstitial nephritis	IN
Mid Arm Muscle Circumference	MAMC
Multisystem disease	MS
Myocardial Infarct	MI
Parathyroid Hormone	PTH
Peripheral Vascular Disease	PVD
Renal Replacement Therapy	RRT

Scottish Renal Registry	SRR
Subjective Global Assessment	SGA
Triceps Skin Fold	TSF
United Kingdom Renal Registry	UKRR
United States Renal Data System	USRDS
Urea Reduction Ratio	URR

Chapter 1
Introduction

1.1 Dialysis patients die early

Patients with end stage renal disease (ESRD) must be treated with dialysis or a kidney transplant to extend their life expectancies. The principle of dialysis was discovered in 1854 by Thomas Graham of Glasgow. Haemodialysis was performed in man for the first time in 1924 by Hass. Willem Kolff developed the first functioning artificial kidney in 1943-1945. Belding Scribner started the world's first outpatient dialysis facility in 1962. Haemodialysis became a practical treatment for kidney failure in 1960s, and is the most common method used to treat advanced and permanent kidney failure. Peritoneal dialysis is the other modality of dialysis that became more safe and convenient to use in the late 1970s and early 1980s (edren.org).

Although maintenance dialysis prevents death from uraemia, patient's survival and quality of life remain an important issue. Despite the improvement in dialysis technology, the advances achieved in general nephrology, and overall improvements in healthcare, dialysis patients carry higher rates of mortality than the normal population. The mortality of dialysis patients is highly influenced by cardiovascular disease (CVD), age, and comorbidity. According to reports from the United States Renal Data System (USRDS), the first year mortality rate is still higher than 20% in dialysis patients and 60% at 5 years. The five year mortality for young patients <65 years was 34% compared to 79% for patients at 56 years or over (USRDS, 2007). The most recent figures of mortality excluding death during the first 90 days in the UK was 19% at one year, and 55% at 5 years. The five year mortality was 35% for young patients and 76% for patients at 65 years or older (Ansell et al., 2007). Foley and colleagues (1998) compared the CVD mortality by age, race, and gender in the general population and dialysis patients (Figure 1.1) and they showed that mortality due to CVD was 10 to 30 times higher in dialysis patients than in the general population.

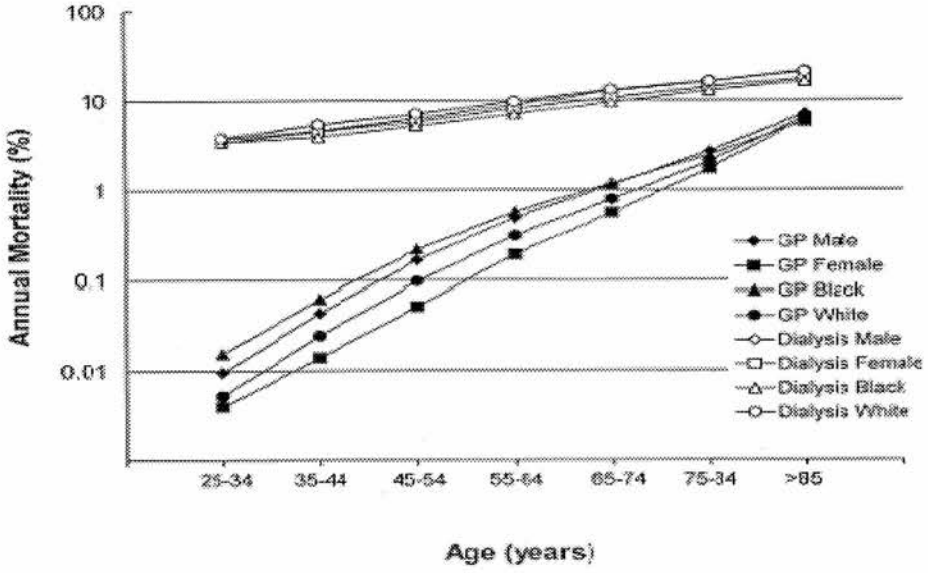

Figure.1.1; Data from general population are from National Center for Health Statistics multiple cause of mortality file 1993. Data from dialysis patients include haemodialysis and peritoneal dialysis combined from USRDS 1994-1996. The cardiovascular mortality is defined as death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary oedema (from Foley et al., 1998).

1.2 Causes of Death

The major causes of death in haemodialysis patient are: cardiovascular disease, infection, and withdrawal from dialysis (Bloembergen et al., 1994; Cohen et al., 1995; Wallen et al., 2001 & USRDS 2002).

1.2.1 Cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death in dialysis patients. It accounts for approximately 50% of deaths in haemodialysis patients (Foley et al., 1998). Cardiovascular mortality is 10 to 30 fold higher than that seen in general population (Sarnak et al., 2000; Churchill et al., 1992). A dialysis patient aged 25 to 44 years is at similar absolute risk of death from cardiovascular disease as an individual without renal disease aged over 75 years (Foley et al., 1998). The increased cardiovascular risk in dialysis patients is not fully clear but it could be explained by: -

1. Higher prevalence of traditional cardiovascular risk factors such as: -

I. About 40% of patients starting RRT are diabetic in the USA and 22% in the UK (USRDS 2007; Ansell et al., 2007).

II. Hypertension is present in about 50–90% of dialysis patients, whereas the frequency of hypertension in age- and sex matched control subjects of the general population does not exceed 25% (Zoccali 2000).

2. Increase occurrence of non traditional risk factors related to chronic kidney disease including: -

I. Coronary arteries, heart valves and myocardium become calcified in dialysis patients, which is associated with increased cardiovascular mortality (Braun et al., 1996; Young et al., 2005).

II. Anaemia is a commonly present in patient starting dialysis treatment and may contribute to development of left ventricular hypertrophy which was found an independent risk factor for survival in dialysis patients (Harnett et al. 1994; Silberberg et al., 1989).

III. Hyperhomocysteinemia in dialysis patients may contribute to increase incidence of cardiovascular morbidity and mortality (Mallamaci et al., 2002; Botsom et al., 1997; Moustapha et al., 1998).

However, hypertension, hypercholesterolemia and higher levels of homocysteine may interact with other non traditional risk factors such as inflammation, comorbidity and malnutrition, thereby altering their overall association with cardiovascular disease in dialysis patients producing a concept known as reverse epidemiology (discussed in 1.3.1.9.4).

3. Some have suggested that inflammation accelerate atherogenesis in dialysis patients (Lindner et al., 1974; Amann et al., 2004). However, whether the atherogenesis of dialysis patients is accelerated and whether the nature of atherosclerosis is similar in haemodialysis patients and the general population remain matters of debate.

4 Cardiovascular diseases may lead to renal hypoperfusion increasing the risk of concurrent renal failure.

5. Factors that predispose to cardiac disease also confer susceptibility to ESRD, therefore these diseases are most likely to co-exist.

1.2.2 Infections

Infections are responsible for approximately 15 to 20% of deaths and are usually due to common organisms (such as staphylococcus aureus) and are often related to the transcutaneous access necessary for both haemodialysis and peritoneal dialysis patients (USRDS 2002; Ansell et al., 2003). An infectious aetiology was responsible for 201 deaths, or 23.1% of all deaths in the HEMO study that included 1846 randomized chronic haemodialysis patients. 871 patients died in this study, providing an annual death rate of 16.6%. The annual rate of infection-related death was 3.8%. There were 1698 infection-related hospitalisations, yielding a 35% annual rate (Allon et al., 2003). Increased infection rate in dialysis patients seems to be due to a variety of predisposing factors including uremic immunosuppression malnutrition, and type of vascular access (Allon et al., 2003)

1.2.3 Withdrawal from dialysis

Withdrawal of long term dialysis in patients with ESRD occurs frequently, and accounts for approximately 15 to 25% of all yearly deaths among the chronic dialysis population in the United States (USRDS 1995 & Cohen et al., 2003). It is the second or third cause of death in such patients (Mailloux et al., 1993 & Bajwa et al., 1996). Several patient factors are associated with the decision to withdraw from dialysis including (Bajwa et al., 1996; Moss et al., 1994 & Leggat et al., 1997):

- Advanced age
- Diabetes mellitus and related vascular complications
- Extensive atherosclerotic disease
- Increasing comorbidity including non-renal terminal illness
- White race
- Female gender

- Higher physical discomfort
- Higher educational level

Withdrawal rate is high among elderly dialysis patients. In one study, for example, dialysis was discontinued in about 6% of patients younger than 65 years of age, but in 14% of those over 65 years of age (Nelson et al., 1994). In another report, 56% of those over the age of 85 died because of withdrawal from chronic dialysis (Neu et al., 1986).

1.3 Factors associated with survival of patients on dialysis

These can be divided into 2 groups of risk factors **(Figure 1.2)**:

1. Risk factors not related to dialysis procedure
2. Risk factors related to dialysis procedure

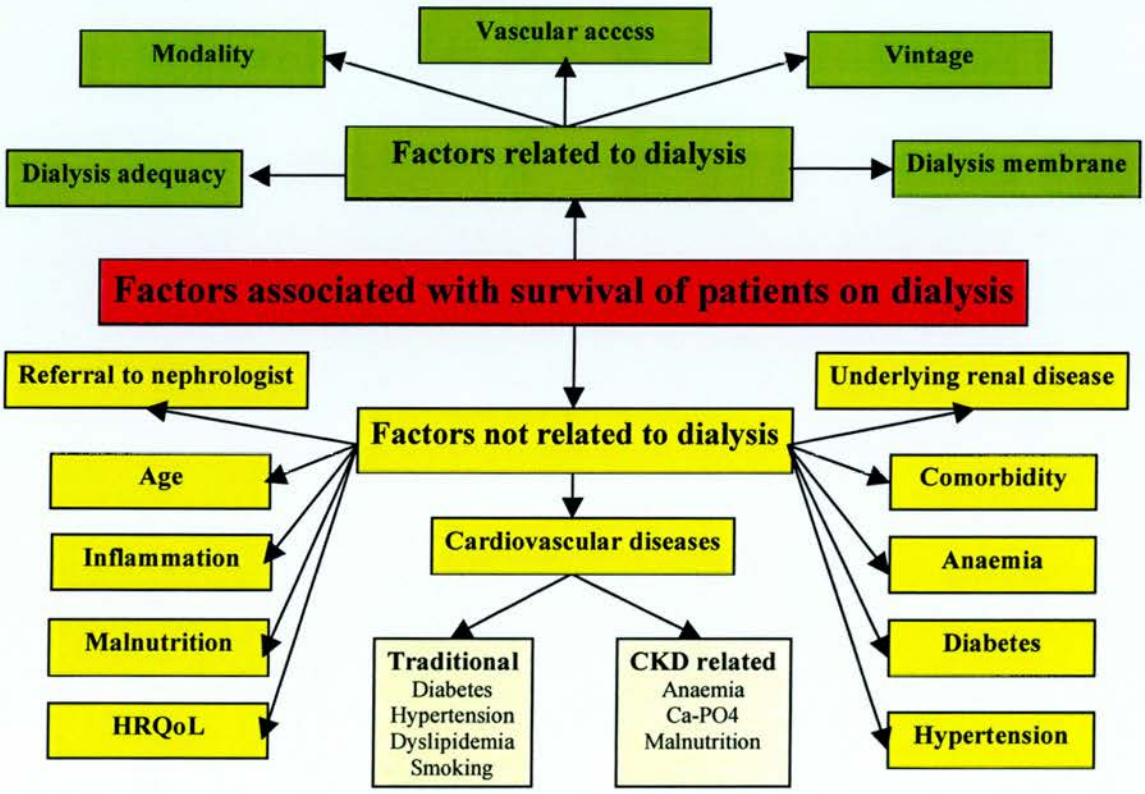

Figure 1.2; Summary of factors associated with survival of patients on dialysis
HRQoL=health related quality of life, Ca-PO4= calcium phosphate metabolism

1.3.1 Risk factors not related to dialysis procedure

1.3.1.1 Age

Age is the most important of the demographic factors associated with increased morbidity and mortality in ESRD. The mean age of new patients starting RRT is between 60 and 65 years in the United States, Europe, Canada, and Japan. As expected survival declines with increasing age, with patients under age 45 doing best; this may be because with older age patients there is an increase in the prevalence of comorbid diseases such as vascular disease and diabetes, which could contribute to further increasing in the risk of cardiovascular death (Mailloux et al., 1994; Charra et al., 1992). An annual report from USRDS (2005) stated that mortality rate of dialysis patients advances more dramatically with age than do the rates of transplant, chronic kidney disease (CKD), and non CKD patients. The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) report (2004) compared the expected remaining lifetime in Europe and USA whites among 3 different groups (general population, transplant, and dialysis patients) and showed that the differences in life expectancy become less with advanced age (Figure 1.2). The UKRR (2005) reported that for every 10 year increase in patient age, there is an increase in the hazard of death in the year after 90 days of 41% (Ansell et al., 2005).

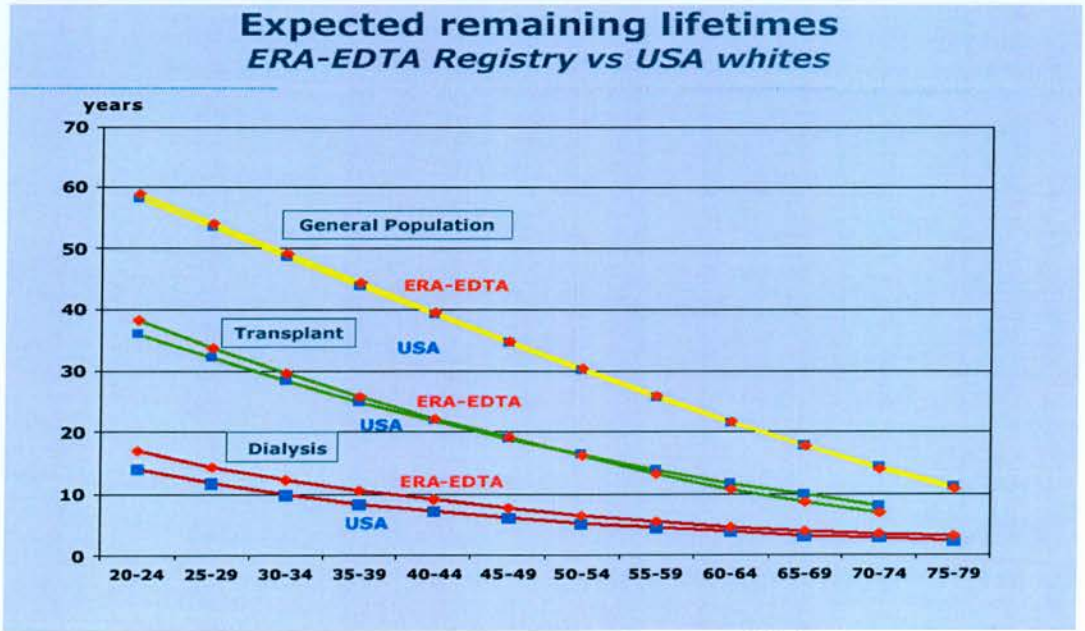

Figure.1.3; ERA-EDTA Registry report 2004

Mailloux and colleagues (1994) analysed the survival of 683 patients who started renal replacement therapy (RRT) between 1970 and 1989, and found fourfold increase in the risk of death between a starting age of 25 and 65 years, with median survival decreasing from 122 months in the youngest to 29 months in the oldest age group. Also an analysis of the survival of about 90.000 patients included in the United States Medicare Program who began dialysis at age of 55 years or more between 1982 and 1987 found that the benefit of chronic haemodialysis (defined as years of extended life) diminished with advanced age, regardless of the cause of renal failure (Byrne et al., 1994). Data from the Canadian Institute of Health Information (1999) showed that the comorbidity rate increases with age and that 80% of individuals more than 65 years of age have at least one other chronic illness at time of initiation of RRT.

1.3.1.2 Race

Survival of patients in the United States varies with race. African-Americans and Asian-Americans have a lower mortality rate than whites (USRDS, 2002; Wong et al., 1999 and Tanna et al., 2000). In one study (based upon the 1995 USRDS report), the survival rates of black, white and other races at five years were 35, 25 and 32 percent, respectively. Similar relative results were observed in a single centre, which reported 47 and 36% survival rates at five years for black and white patients respectively (Bleyer et al., 1996). The survival advantages persist after careful adjustment for unique patient characteristics, comorbidities, and laboratory abnormalities (Wong et al., 1999; Tanna et al., 2000; and Bleyer et al., 1996).

1.3.1.3 Underlying renal disease

Significant differences in outcome are associated with underlying disease. Five year survival among dialysis patients is best with chronic glomerular disease and polycystic kidney disease, intermediate with hypertension-induced renal disease, and worst with diabetic nephropathy (Mailloux et al., 1994). Patients with renovascular disease also have poor prognosis; the risk of mortality in these patients is double that of patients with other renal diseases (excluding diabetes), and the survival estimate at 5 and 10 years are 16 and 8 percent respectively (Mailloux et al., 1994).

1.3.1.4 Comorbidity

In the HEMO study, comorbidity was defined as all medical problems other than the cause of renal disease (Miskulin et al., 2001).

1.3.1.4.1. Comorbidity and outcome

Comorbid medical conditions are frequently seen in dialysis patients and have an important effect on clinical outcomes, including death, hospitalisation, and quality of life. The UKRR (2005) reported that comorbidity is a powerful predictor of early and late mortality among patients starting RRT (Ansell et al., 2005). The influence of comorbidity on outcomes in dialysis patients have been addressed in a number of observational studies. Wright (1991) showed that survival in RRT was significantly influenced by the presence of cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease and cancer. Davies and coworkers (1995) in a study of 97 peritoneal dialysis patients found a strong effect of comorbid disease on mortality. Khan and colleagues (1996) also found that survival in 1407 patients in seven centres in five European countries was similarly influenced by the presence of comorbidity. Chandna and collaborators (1999) found that comorbid conditions are important in predicting survival and morbidity of patients on dialysis. The presence of diseases such as cardiac disease, cerebrovascular disease, diabetes, atherosclerosis, and malignancy have been recognized to play a big role in increasing the mortality risk in ESRD patients (Shapiro et al., 1983; Khan et al., 1993). Data from Dialysis Outcome and Practice Pattern Study (DOPPS) (2003), which compared demographic characteristics and comorbid conditions of 17236 haemodialysis patients across Europe, Japan, and US, showed that increasing age and a variety of comorbid conditions (coronary artery disease, congestive heart failure, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, lung disease, cancer, gastrointestinal bleeding, HIV infection, neurologic disease and hepatitis) were associated with higher mortality (Goodkin et al., 2003).

1.3.1.4.2 Comorbidity Assessment

There is no consensus on the measurement and grading of comorbid illnesses in dialysis patients. However, several comorbidity indices have been developed and

modified specifically for dialysis population. Each has been validated for outcome of mortality in the dialysis population, with a graded increase in mortality risk predicted per increment in instrument level (Charlson et al., 1987; Wright et al., 1991; Khan et al., 1993; Nicolucci et al., 1992; Beddhu et al., 2000; and Davies et al., 2002).

1.3.1.4.3 Charlson comorbidity index

The Charlson Comorbidity index (CCI) was developed in 1987 based on one year mortality data from internal medicine patients. It was initially validated in a cohort of patients with breast cancer. The index consists of 19 medical conditions which are primarily defined using International Classification of Diseases Ninth Revision diagnosis codes (ICD-9-CM); each condition is weighted 1–6 with total scores ranging from 0–37 (Table.1.1). From the weighted conditions, a sum score represents the total comorbidity score. To account for the effects of increasing age, one point can be added to the CCI score for each decade of life over the age of 50 (Charlson et al., 1987). CCI is a widely used tool in areas other than ESRD and has been found to predict survival in patients treated both by peritoneal dialysis (Fried et al., 2001), and haemodialysis (Beddhu et al., 2000).

Score	Condition	Score	Condition
1	Myocardial infarct	2	hemiplegia
1	Congestive heart disease	2	Moderate or severe renal disease
1	Peripheral vascular disease	2	Diabetes with end organ damage
1	Cerebrovascular disease	2	Any tumour
1	Dementia	2	Leukaemia
1	Chronic pulmonary disease	2	Lymphoma
1	Connective tissue disease	3	Moderate or severe liver disease
1	Ulcer disease	6	Metastatic solid tumour
1	Mild liver disease	6	Acquired immunodeficiency syndrome AIDS
1	diabetes		

Table.1.1; Charlson comorbidity scores

1.3.1.4.4 Khan score

This is a combination of age and comorbidity, used to assign patients to one of three risk groups; low, medium, and high risk (Khan et al., 1993). Patients over 80 years are always classified in the high risk group. Patients between 70 and 80 years are allocated to the medium or high risk group (Table 1.2) (Khan et al., 1993).

Grade-0 (low risk)	Age<70 years and no comorbid disease
Grade-1 (medium risk)	Age 70-80 years, or <70 years age with any one of the following: Angina, previous myocardial infarction, cardiac failure, chronic obstructive airway disease, pulmonary fibrosis, or liver disease (cirrhosis, chronic hepatitis), peripheral vascular and cerebrovascular diseases or <70 with diabetes mellitus
Grade-2 (high risk)	Age>80 years, or <80 years with two or more organ dysfunction, cardiopulmonary disease, visceral malignancy, or 70-80 years with diabetes or cardiopulmonary disease.

Table.1.2; Khan comorbidity risk groups

1.3.1.4.5 Davies score

This is based on the presence or absence of seven comorbid conditions (malignancy, ischaemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes, systemic collagen vascular disease and pulmonary diseases) (Table 1.3), also producing three risk groups (Davies et al., 1995 and 2002). Unlike other indices age is not included in this index, because it was specifically designed to be used in conjunction with age as an independent covariate. Patients without comorbid conditions are classified as low risk, patients with one or two comorbid disease are regarded as medium risk. Patients with three or more comorbid conditions are classified as high risk patients (Davies et al., 1995 and 2002).

Ischemic heart disease (defined as prior MI, angina, or ischemic changes on ECG)
Left ventricular dysfunction (defined as history of congestive heart failure, pulmonary oedema not due to error in fluid balance)
Peripheral vascular disease
malignancy
Diabetes mellitus
Collagen vascular disease
Other significant pathology (chronic obstructive pulmonary disease)

Table 1.3; Davies comorbidity conditions

van Manen and colleagues (2002) found that Charlson, Khan, and Davies indices had similar prognostic value with respect to mortality in ESRD patients. Furthermore, they found that a comorbidity index that included severity grading of several diseases did not perform better than the Charlson, Khan and Davies indices. Also the same group in the Netherlands Cooperative Study on Dialysis Adequacy (NECOSAD study), an observational cohort study involving 1041 incident dialysis patients from 36 centers in the Netherlands, evaluated the accuracy of these indices when taking the health status as an outcome measure and they found that the three indices performed equally with respect to their association with health status. However, they favoured the Davies index because it required the least variables to be recorded to score it (van Manen et al., 2003).

1.3.1.5 Anaemia

Anaemia remains a common finding in dialysis patients. The UKRR (2005) reported that 40% of individuals new to dialysis had a haemoglobin <10g/dl (Ansell et al., 2005). Haemodynamic changes in anaemia include increased preload, heart rate and stroke volume as well reduced afterload all act to raise cardiac output (Duke et al., 1969). Over time these compensatory mechanisms lead to eccentric left ventricular hypertrophy.

There is no convincing evidence for a specific target level of haemoglobin. The appropriate target haemoglobin concentration has been debated almost since recombinant human epoetin first became available.

The observational data suggest a high haemoglobin level (>13 g/dL) associated with lower rates of hospitalisation and mortality (Collins et al., 2001; and Ma et al., 1999; and Li et al., 2004) and haemoglobin level (<10 g/dL) [haematocrit <30%] increase the risk of mortality (Madore et al. 1997; Locatelli et al., 1998; Ma et al. 1999; and Locatelli et al., 2004). These observational studies have limitations because of their retrospective design and the potential effect of confounding factors.

However, randomized controlled studies failed to show reduction in mortality when aiming for a haemoglobin level of >12 g/dl. The CHOIR and CREATE randomized trials included 1432 and approximately 600 patients with CKD respectively. They showed either risk or no benefit with regard to cardiovascular outcomes aiming to completely correct the haemoglobin in CKD patients (Singh et al., 2006; and Drueke et al., 2006). Also the Canada-Europe study, which included 596 incident haemodialysis patients, showed a higher rate of cerebrovascular acceident in the higher haemoglobin group (13 g/dl) versus lower haemoglobin group (11 g/dl) (Parfrey et al., 2005). However, normalization of haemoglobin was shown to be associated with improved quality of life in terms of main physical symptoms, fatigue, depression and frustration as evaluated by Kidney Disease Questionnaires (Furuland et al., 2003; Drueke et al., 2006).

International guidelines have recommended different target haemoglobin concentrations. The first National Kidney Foundation Kidney Disease Outcomes Quality Initiative anaemia guidelines, published in 1997 (K/DOQI 1997a) and updated in 2001 (K/DOQI 2001a), called for a 11–12 g/dl target haemoglobin range. In May 2006 the guidelines were changed to an effective target range of 11–13 g/dl (K/DOQI 2006). The European Best Practice Guideline 5 (2000) set a minimum target of haemoglobin 11g/dl, with an average value of 12-12.5g/dl. The UK Renal Association recommended that individuals with chronic renal failure should achieve haemoglobin of 10g/dl within 6 months of being seen by a nephrologist unless there

is a specific reason why it could not be achieved. The above recommendation more likely to be refined or changed as further big randomized controlled studies examining the benefit of higher versus lower target haemoglobin concentrations are published.

1.3.1.6 Diabetes Mellitus

The number of patients who have diabetes and ESRD and are being treated with RRT is increasing dramatically, to the point that, during the past few years, in many countries, diabetes has or will soon become the most frequent single cause of ESRD. According to USRDS, the annual number of patients who have diabetes and are admitted to RRT in the United States more than doubled between 1995 and 2000 (from 19155 to 41685 patients), and there was a striking increase in the percentage of incident ESRD patients with diabetes as the primary renal diagnosis (30.4% in 1987, 36.3% in 1992, and 45.2% in 2000) (USRDS 2002). As a consequence of the increasing number of patients who have diabetes and are being admitted to RRT and their improved survival, the prevalence of RRT patients with diabetes has also significantly increased worldwide; in the US, the proportion of RRT patients with diabetes as the cause of ESRD increased from 26.9% in 1991 to 30.6% in 1995 and 36% in 2000 (USRDS 2002)

Patients with diabetes receiving RRT continue to do worse with respect to survival and QoL than do non-diabetic patients (Wolfe et al., 1992; and USRDS, 2003). According to USRDS (2002), the adjusted 5-year survival of patients who have diabetes and started RRT in 1995 was 33.6% (it was 24.5% for patients who started dialysis in 1985); significantly worse than that of patients in whom primary cause of ESRD was hypertension (42%), glomerulonephritis (53%), or other renal disease (43%). The main reason for such high mortality rates, which is of cardiovascular origin in the majority of cases (Koch et al., 1993), is that the cardiovascular conditions of patients with diabetes are already severely impaired when they start RRT, as demonstrated by the high prevalence of coronary artery disease, stroke, peripheral vascular disease, and amputations (Stack et al., 2001; and Eggers et al., 1999). This explains why patients who have diabetes and are on RRT are at higher

risk of developing de novo cardiovascular disease, particularly ischaemic heart disease, which not only is more frequent but also has a more aggressive course than in non-diabetic patients (Herzog et al., 1998). Survival also varies inversely with age, being best in young diabetics with good blood pressure control and no clinically evident cardiac disease (USRDS, 2003; and Locatelli et al., 2003). The USRDS 2003 report showed that extended survival at 10 years appears to be less likely for diabetic as compared to non-diabetic patients (4% versus 11 to 14%).

1.3.1.7 Hypertension

Hypertension is a common finding in dialysis patients. Based upon multiple studies, over 50 to 60% of haemodialysis patients are hypertensive. These values are much lower than the 80% incidence of hypertension at the initiation of dialysis, due largely to better volume control in most patients (Zuccala et al., 1988). The relationship between blood pressure and mortality in dialysis patients remains controversial. There has been considerable discussion regarding whether hypertension is a risk factor for mortality, whether hypotension is associated with increased cardiovascular mortality, and how much blood pressure must be lowered to minimize mortality.

High blood pressure in the general population is associated with increased cardiovascular mortality and morbidity, and its control can reduce these adverse consequences (Sytkowski et al., 1996). Unlike the general population, observational studies showed that haemodialysis patients have a higher mortality rate with a low blood pressure whereas survival advantages shown to be associated with a high blood pressure, what is termed as reverse epidemiology (Kalantar-Zadeh et al., 2003b). One study of 5433 haemodialysis patients found that, low systolic blood pressure <110 mmHg pre and post dialysis was associated with increased overall and cardiovascular mortality (Zager et al., 1998). Another report of nearly 4500 haemodialysis patients also found a significantly increased mortality risk among patients with low pre-dialysis systolic blood pressure (110 mmHg) (Port et al., 1999). On the other hand, a relation between hypertension and increased mortality was observed (Charra et al., 1992; Fernandez et al., 1992). in a study of 11142 haemodialysis patients from the USRDS dialysis morbidity and mortality waves 3

and 4 study found that high post dialysis systolic blood pressure values were associated with increased mortality and use of anti-hypertensive medication showed a strong association with survival (Foley et al., 2002).

The inverse relation between blood pressure and mortality has resulted in questioning whether treatment goals for hypertension control in dialysis patients should be different from the general population. It would appear not reasonable to accept uncontrolled hypertension in dialysis patients. Observational studies showed that adequate blood pressure control may lead to reduction of cardiovascular events especially congestive heart failure and regression of left ventricular hypertrophy (Nakamura et al., 2005; London et al., 2001) and furthermore, optimal blood pressure control is associated with high survival rates (Charra et al., 1992; Foley et al., 2002). In general, treatment goals of hypertension should not based on observational studies. Prospective randomised studies are needed to compare the effect of different blood pressure targets on outcome in dialysis patients.

1.3.1.8 Cardiovascular disease

At onset of dialysis heart disease is very common; around 44% (Foley et al., 1995). Cardiac disease is the leading cause of death among prevalent maintenance dialysis patients. About half the deaths in dialysis patients are attributed to CVD (USRDS, 1998). In addition, dialysis patients with cardiac disease have a higher case-fatality rate than non dialysis patients with heart disease. Cardiovascular morbidity is also high, accounting for about one third of the hospitalisations of dialysis patients (USRDS, 1998). This excess in cardiovascular morbidity and mortality is, in part, caused by high prevalence of cardiac disease before initiation of dialysis (Foley et al., 1995), the high prevalence of cardiovascular risk factors in patients with progressive CKD and to the contribution of diabetes and hypertension in the aetiology of ESRD (USRDS 2003).

1.3.1.8.1 Risk factors for cardiovascular morbidity and mortality

These can be divided into 2 major groups

1. Traditional risk factors (diabetes, hypertension, dyslipidemia, age and smoking).
2. Factors related to chronic kidney disease (anaemia, abnormality of calcium-phosphate metabolism [secondary hyperparathyroidism], and malnutrition)

1.3.1.8.1.1 Traditional risk factors

1.3.1.8.1.1.1 Diabetes Mellitus

In ESRD it is widely recognised that diabetic patients are at a very high cardiovascular risk. At commencement of dialysis, diabetes was strongly associated with concentric left ventricular hypertrophy, ischaemic heart disease, and cardiac failure compared with non diabetics (Foley et al., 1997). In addition, it was associated with the development of de novo ischaemic heart disease (Foley et al., 1997) (diabetes was discussed more in 1.3.1.6)

1.3.1.8.1.1.2 Hypertension

Hypertension was discussed in 1.3.1.7.

1.3.1.8.1.1.3 Dyslipidemia

Disturbance in plasma lipoprotein metabolism is frequently observed among patients with ESRD, particularly those on dialysis. The combination of dyslipidemia and other co-existing risk factors such as hypertension and diabetes is likely to contribute to a marked increase in the risk of cardiovascular morbidity and mortality in individuals receiving dialysis (Foley et al., 1998).

Dyslipidemia in haemodialysis patients is characterized by: i) increased concentration of plasma triglycerides rich apoB containing lipoproteins. They occur preferentially in very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low density lipoprotein (LDL). ii) Reduced concentration of apoA containing lipoprotein mainly apoA-I and apoA-III. They occur preferentially in high density lipoprotein (HDL). iii) Increase in apoC-III and apoE concentrations

(Attman et al., 1999). The apolipoprotein profile of peritoneal dialysis patients is characterized by a proportionately greater increase in the level of apoB, apoC-III, and apoE than in haemodialysis patients (Johansson et al., 2000). The principal disturbance of the lipoprotein metabolism appears to be a reduced catabolism and clearance of triglyceride rich apoB containing lipoproteins (Attman et al., 1993).

Observational studies in dialysis patients have shown that low, rather high cholesterol is a marker of high risk in these patients, possible because low cholesterol reflects malnutrition (Lowrie et al., 1990). Liu and colleagues (2004) suggested that a low cholesterol level is considered as a marker of malnutrition in dialysis patients as they found that cholesterol levels are related to the nutritional status of dialysis patients (Liu et al., 2004). Data from USRDS (2003) showed that low serum cholesterol is associated with an increased risk of death. Also decreased cholesterol may be a marker of inflammation (see section 1.3.1.9.2).

Statin treatment has been proven to reduce the mortality and morbidity in cardiovascular disease in patients with normal renal function (4S, 1994; WOSCOPS, 1995; MRC/BHF, 2002). Meta-analysis of 14 trials including 90,000 participants showed a clear benefit from statins for both primary and secondary prevention, but too few patients with CKD were included in these trials (Baigent et al., 2005).

There is no definitive evidence that statins significantly reduce cardiac death in patients on RRT. The Assessment of Lescol in renal transplantation (ALERT) study compared Fluvastatin versus a placebo showed that there was no significant reduction in cardiac death and myocardial infarction over 6 years follow-up (Holdaas et al., 2001). The cholesterol and Recurrent events (CARE) study showed Pravastatin 40mg reduced further cardiac events in patients with previous myocardial infarction and mild CKD (Tonelli et al., 2003). The Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival study (CHORUS) was initiated using Cerivastatin in haemodialysis patients, but stopped in 2001 when Cerivastatin was withdrawn from the market.

The Die Deutsche Diabetes Dialysis Study (4D study), a double blind controlled trial randomised 1255 patients with type 2 diabetes receiving maintenance haemodialysis, to receive 20 mg of atorvastatin per day or matching placebo showed surprising results as the primary end point of cardiovascular death, was only reduced by 8% which was not statistically significant. The 4 D investigators concluded that dialysis patients mainly die from cardiovascular deaths other than due to coronary artery disease precipitated by hypercholesterolemia, or the negative results might have been due to the advanced cardiovascular diseases in the chronic haemodialysis patients, and because statin therapy was initiated too late (Wanner et al., 2005). In contrast, the CARDS trial (Collaborative Atorvastatin Diabetes Study) of 2838 patients with type 2 diabetes who had not yet developed significant kidney disease to assess the effectiveness of atorvastatin 10 mg daily for primary prevention of major cardiovascular events showed that atorvastatin reduced the rate of acute coronary events by 36%, coronary revascularization by 31%, stroke by 48%, and death by 27% (Colhoun et al., 2004). It is reasonable to continue using statin until further evidence is available that confirms the results of the 4D study in larger numbers of dialysis patients including those non diabetic and peritoneal dialysis patients.

Work to find a clear evidence of statins beneficial effect on survival of dialysis patients is still ongoing. The Study of Heart and Renal Protection (SHARP) was designed to assess the effects of lowering cholesterol on major vascular events, and on the rate of progression to ESRD among patients with CKD. SHARP aims to compare Ezetimibe (cholesterol absorption inhibitor)/Simvastatin (cholesterol lowering therapy) versus placebo among 9000 patients with CKD (3000 on dialysis). Results are expected in 2009. The AURORA study is evaluating the use of Rosuvastatin (10mg versus placebo) in 2700 regular haemodialysis patients and assessment of survival and cardiovascular events. The AURORA results are expected in 2008.

1.3.1.8.1.1.4 Smoking

Smoking is an important CVD risk factor. Recently, it has been implicated in the progression of CKD in patients with severe hypertension (Regalado et al., 2000). The Cardiovascular Risk Extended Evaluation in Dialysis (CREED) study, which investigated the relationship between carotid atherosclerosis and some major cardiovascular risk factors in patients on chronic dialysis, recruited 119 unselected dialysis patients (89 on haemodialysis and 30 on peritoneal dialysis). In a detailed echo-colour Doppler study of the carotid arteries of this cohort, they found that arterial pressure and smoking were associated with carotid atherosclerosis, independent of the other risk factors (Malatino et al., 1999). Smoking appears to be especially harmful in diabetic ESRD patients. In one study it was associated with a doubling of mortality rates (McMillan et al., 1990). In a study comparing survival rate in 22 diabetic haemodialysis patients who smoked >10 cigarettes/day with that in 30 non smoking haemodialysis diabetic patients, five year survival was 9% and 30% in the smokers and no smokers, respectively (Biesenbach et al., 1996).

1.3.1.8.1.2 Factors related to chronic kidney disease

1.3.1.8.1.2.1 Anaemia

Anaemia was discussed in 1.3.1.5.

1.3.1.8.1.2.2 Abnormality of calcium – phosphate metabolism

Renal osteodystrophy is a common complication of CKD and is believed to have its origins early in the onset of renal impairment (Coburn 1980). Elevations of parathyroid hormone (PTH) in serum have been reported in patients with only slightly abnormal GFR of 60 to 80 ml/min (Slatopolsky et al., 1985 and Baker et al., 1989). The skeletal manifestations vary from patient to patient, but essentially fall into 2 groups [high-turnover lesions (osteitis fibrosa and mild hyperparathyroid disease) and low-turnover lesions (osteomalacia and adynamic)], and, in children, retardation of growth. Extra-skeletal manifestations of this syndrome, such as myopathy, vascular and visceral calcification, and peripheral ischaemic necrosis, are also well recognized (Block et al., 2004 and Young et al., 2005).

However, over the past 10 years, it has become apparent that there is a strong association between serum phosphate levels, vascular disease and increased mortality in dialysis patients. Block and colleagues (2004) showed that hyperphosphataemia and hyperparathyroidism were significantly associated with all-cause, cardiovascular, and fracture-related hospitalisation in haemodialysis patients. Ganesh and collaborates (2001) found that serum phosphate >2.10 mmol/L (6.5 mg/dl) phosphate was significantly associated with increased relative risk of death from coronary artery disease and sudden death. An observational study describes the significant predictors, and consequences of abnormal calcium–phosphate metabolism in representative groups of 307 haemodialysis facilities which enrolled 17236 patients participating in the DOPPS study. This showed that all-cause mortality and cardiovascular mortality were significantly associated with serum concentrations of phosphate, calcium, calcium-phosphate product and PTH (Young et al., 2005). The UK Renal association recommended serum phosphate maintained between 1.1 and 1.8 mmol/l and calcium phosphate product should be kept below 4.8 $mmol^2/L^2$ and ideally below 4.2 $mmol^2/ L^2$. The K/DOQI guidelines (2003) recommended that serum phosphate should be between 1.13 and 1.78 mmol/L (3.5 and 5.5mg/dL) and calcium phosphate products upper limits of $55mg^2/dL^2$.

Observational studies showed the association between serum calcium level and increased morbidity and mortality. In a study of 433 patients commencing dialysis (both haemodialysis and peritoneal dialysis) showed low calcium level (mean calcium <2.2 mmol/L (8.8 mg/dL) was significantly associated with increased mortality (RR 2.10). Morbidity was also increased. The relative risk associated with calcium level of < 2.2 mmol/L was 5.23 for de novo ischaemic heart disease, 2.46 for recurrent ischaemic heart disease and 2.64 for recurrent cardiac failure (Foley et al., 1996b). The DOPPS study also showed that mortality of haemodialysis patients is associated with serum calcium (Young et al. 2005). The UK Renal Association recommended serum calcium maintained between 2.2 and 2.5 mmol/L whereas the K/DOQI guideline is unique in recommending that serum calcium be maintained in the lower half of the normal range (2.10 to 2.37mmol/L [8.4 to 9.5mg/dL]). However, no randomized trials support the hypothesis that a decrease in serum

phosphate or calcium levels toward the normal or target level might be associated with decreased mortality. The long-term effects of this on serum PTH and mortality are unknown and no randomized trial has ever tested the guideline.

1.3.1.8.1.2.3 Malnutrition

Malnutrition is discussed more in 1.3.1.10

1.3.1.9 Inflammation

Inflammation has been identified as an epidemiologically important risk factor for cardiovascular disease in the general population (Ridker et al., 1998). In CKD patients elevated levels of inflammatory markers have been shown to be associated with increased all cause and cardiovascular mortality (Zimmermann et al., 1999; Yeun et al., 2000; Stenvinkel et al., 2002; Wang et al., 2003; Menon et al., 2005; and Mallamaci et al., 2005). Several inflammatory biomarkers, such as serum albumin (Lowrie et al., 1990), CRP (Zimmermann et al., 1999; and Yeun et al 2000), interleukin (IL)-6 (Kimmel et al., 1998; Pecoits-Filho et al., 2002; and Rao et al., 2005), intercellular adhesion molecule (ICAM)-1 (Suliman et al., 2006), neutrophils count (Pifer et al., 2002), IL-18 (Chiang et al., 2004), and fibrinogen (Zoccali et al., 2003) predict hospitalisation and outcome in patients with ESRD.

1.3.1.9.1 C-reactive protein (CRP)

CRP is a well established acute phase reactant. It has a pentameric structure with a molecular weight of 115 kDa. Its physiological function is not fully understood, but it may play a role in the clearance of endotoxins and opsonized bacteria. It increases during many conditions such as infections and recent surgery.

In the general population CRP is found to be related to the risk of myocardial infarction, stroke and sudden death (Ridker et al., 1997). Since the Bergstrom and colleagues report (1995) of an association between elevated CRP and outcome, several studies have found an independent association between CRP levels and both all cause and cardiovascular mortality in CKD (Menon et al., 2005) as well as ESRD patients treated with haemodialysis (Ikizler et al., 1999; and Yeun et al., 2000) or

peritoneal dialysis (Noh et al., 1998; and Ducloux et al., 2002). Zimmerman and colleagues (1999) monitored mortality in 280 stable haemodialysis patients over a 2 year observational period and found that all cause and cardiovascular mortality rate have been increased with increasing quartiles of CRP. Patients with CRP levels in the highest quartile >15.7 mg/dl experienced almost a 5-fold increase in all cause and cardiovascular mortality compared with patients who had CRP levels less than 3.3mg/dl. This effect was independent of several other known mortality predictors. This study strongly agrees with Iseki and coworkers (1999) study which included 163 haemodialysis patients and again showed that high CRP levels are a strong predictor of death in chronic dialysis patients. Recent experimental work showed therapeutic inhibition of CRP is a promising new approach to cardio-protection in acute myocardial infarction. Pepys and colleagues (2006) found that administration of CRP binding inhibitor [1,6-bis(phosphocholine)-hexane] to rats undergoing acute myocardial infarction stopped the increase in infarct size and cardiac dysfunction produced by injection of human CRP (Pepys et al., 2006).

1.3.1.9.2 Inflammation and malnutrition

The association between malnutrition and inflammation in ESRD patients could be an explanation for malnutrition associated mortality (Kalantar-Zadeh et al., 2001; Kaysen et al., 2002; and Qureshi et al., 2002). Many studies suggested that malnutrition is a consequence of chronic inflammation in patients with renal insufficiency (Kaizu et al., 1998; Yeun et al., 1998; and Stenvinkel et al., 2002). The malnutrition secondary to inflammation could be developed due to elevated levels of pro-inflammatory cytokines that could increase protein degradation, suppress protein synthesis and induce anorexia by suppression of appetite through the anorexic hormone leptin, which at least in animal experiments has been shown to be up-regulated by pro-inflammatory cytokines (Flores et al., 1989; Espat et al., 1994; Grunfeld et al., 1996; and McCarthy et al., 2000). Also the synthesis and serum concentrations of nutritional markers (serum albumin, prealbumin, serum cholesterol and transferrin) decrease during inflammation entirely independently of nutritional state (Ritchie et al., 1999; Lowrie 1998; and Moshage et al., 1987). Stenvinkel and colleagues (1999) established that patients with pre-ESRD who were judged to be

malnourished by measurement of subjective global assessment also had markers consistent with the presence of inflammation. CRP was significantly greater in malnourished patients.

1.3.1.9.3 Malnutrition inflammation and cardiovascular disease

Although malnutrition and inflammation have been reported to be strong predictors of cardiovascular mortality in dialysis patients (Acchiardo et al., 1983; and Owen et al., 1998), they do not appear to be the direct causes of mortality in most patients. Instead, CVD is the most common cause of mortality in this population (Foley et al., 1998), whereas malnutrition may be a direct cause of less than 5% of deaths (ERA-EDTA 1986). A study by Qureshi and colleagues (2002) to assess the importance of nutritional status, inflammation and comorbidity as predictors of mortality in 128 haemodialysis patients showed that malnutrition, inflammation and CVD were all significant independent risk factors for mortality and they suggested that inflammation, malnutrition, and CVD could be interrelated. Moreover, malnutrition and inflammation are associated with a higher cardiovascular mortality in haemodialysis patients (Keane et al., 1994; and Zimmerman et al., 1999).

1.3.1.9.4 Reverse epidemiology

Traditional risk factors (hypertension, obesity and hypercholesterolemia) are predictors of cardiovascular disease in the general population, whereas the reverse is observed in chronic haemodialysis patients. In these individuals, high blood pressure, obesity, and high levels of serum cholesterol levels appear to be associated with a survival advantages (Fleischmann et al., 1999; Zager et al., 1998; and Iseki et al., 2002). Interestingly, reversal back to traditional epidemiology has been described after successful renal transplantation (Kasiske 2000). These contradictory observations, which are in contrast to the well known association between hypercholesterolemia, hypertension, obesity, and poor outcome in the general population, have been referred to as reverse epidemiology (Kalantar-Zadeh et al., 2003b). The aetiology of the switch to the opposite direction in chronic haemodialysis patients is not clear. The reverse epidemiology phenomenon may be related to the presence of malnutrition inflammation and atherosclerosis complex and

its strong impact on outcome in this group of patients. Based on 10 years follow up of 1167 haemodialysis patients, Iseki and his group (2002) reported that patients with hypocholesterolemia had a higher prevalence of elevated CRP and a lower survival. The confounding effect of malnutrition inflammation atherosclerosis syndrome on the association between CVD risk and risk factors, such as hypercholesterolemia and obesity as indicated by high BMI, is apparently able to reverse the associations observed in the general population. The reverse epidemiology phenomenon could be also due to survival bias as patients with CKD who are not on dialysis have a high mortality and small number of these patients reaches ESRD. Therefore, it is possible that selection of survivors leads to a different epidemiology. A study of the natural history of chronic kidney failure which included 28,000 patients (GFR <90ml/min/1.73m^2) showed that the prevalence of hypertension and hyperlipidemia was lower in patients who died before advancing to ESRD than in survivors (Keith et al., 2004).

1.3.1.10 Malnutrition

Malnutrition is common in patients with CKD, with prevalence ranging from 28% to 48% in predialysis patients (Heimburger et al., 2000; and Lawson et al., 2001) and 9 to 72% in dialysis patients (Kopple 1997a; and Stratton et al., 2003). The nutritional status in dialyzed patients is affected mainly by presence of comorbid conditions (CANUSA, 1996).

According to Stenvinkel and colleagues (2000), there are 2 forms of protein energy malnutrition (PEM) in dialysis patients: **type 1,** a more benign form, in which inadequate nutritional intake is the predominant cause, can be effectively treated by increased nutritional intake and with little or no important consequences for clinical outcome. In contrast, **type 2**, a malignant form essentially caused by inflammation and associated with poor clinical outcome. Table 1.4 lists the major groups of measurements (dietary intake, body compositions, scoring system, and laboratory tests) that have been used to assess nutritional status in dialysis patients (Kalantar-Zadeh et al., 2003a). However there is no one agreed measurement that functions well for assessing nutritional status in dialysis patients.

Malnutrition is a common risk factor of poor quality of life and increased morbidity and mortality, including cardiovascular death in maintenance dialysis patients (Kopple 1997b and; Kopple et al., 1999). Malnutrition may be a direct cause of less than 5% of deaths (ERA-EDTA 1986), but the significant relationship between malnutrition and CVD morbidity and mortality in haemodialysis patients has been demonstrated in many studies (Bergstrom et al., 1998; Foley et al., 1996a; Zimmermann et al., 1999; and Kaysen et al., 2001). Moreover, under-nutrition state of maintenance dialysis patients may predispose to infection or other inflammatory processes that may be responsible about association between malnutrition and adverse outcome (Kalantar-Zadeh et al., 2001; and Kaysen et al., 2002). Furthermore, the malnutrition, inflammation and atherosclerosis relationship which was mentioned above could be an explanation for increased mortality in dialysis patients.

1. Nutritional intake • Direct: Diet recalls and diaries, food-frequency questionnaires. • Indirect: based on urea nitrogen appearance: normalized protein nitrogen appearance (nPNA) = normalized protein catabolic rate (nPCR)
2. Body composition • Weight based measures: BMI, weight for height, oedema-free fat-free weight • Skin and muscle anthropometry by calliper: skin-folds, extremity muscle mass • Total body elements: total body potassium • Energy-beam-based methods: Dual Energy X-ray Absorptiometry, (DEXA), Bioelectrical Impedance analysis, (BIA), Near-Infra Red interactance (NIR) • Other energy-beam- related methods: total body nitrogen
3. Scoring System • Conventional Subjective Global Assessment (SGA), and it is modifications (e.g. Dialysis Malnutrition Score), Malnutrition-Inflammation Score (MIS)) • Other scores: Haemodialysis Prognostic Nutritional Index, e.g. (Harty et al, 1994; Merkus et al, 2000)
4. Laboratory values • Serum proteins; Albumin, Prealbumin • Serum creatinine, serum urea nitrogen • Growth factor: IGF-1, leptin

Table.1.4; Assessment tools for evaluation of malnutrition in maintenance dialysis patients (Kalantar-Zadeh et al., 2003a)

1.3.1.11. Malnutrition markers and mortality

The malnutrition and adverse outcome relationship has been demonstrated by several studies where the malnutrition status has been assessed by the following nutritional markers:-

1.3.1.11.1. Serum Albumin

Serum albumin is probably still the most commonly used nutritional marker in ESRD patients. Lowrie and Lew (1990) found a strong inverse relationship between serum albumin and all-cause mortality in a retrospective analysis of more than 12,000 prevalent dialysis patients. The relative risk of death for patients with a serum albumin < 2.5 g/dl was about 20 fold greater compared to patients with a serum

albumin of 4.0-4.5g/dl. The HEMO study group analysis to determine if indicators of nutritional status were associated with subsequent mortality in haemodialysis patients found that elevated serum albumin as independently associated with decreased mortality, especially during early follow up as subjects with low serum albumin values (<3.6 g/dL) had elevated relative risks of mortality compared to the reference (≥4.0 g/dL) (Dwyer et al 2005). Also data analysis from USRDS which included 3607 haemodialysis patients found increased mortality among those with low serum albumin and low body mass index (BMI) (Leavey et al., 1998).

However, serum albumin value has been questioned because a low serum albumin levels may reflect not only poor nutrition, but also albumin losses in urine and/or dialysate, the presence of an inflammatory reaction, systemic diseases, and old age (Heimburger et al., 1994).

1.3.1.11.2. Serum Creatinine

Serum creatinine is useful marker of nutritional status in dialysis patients (K/DOQI, 2000). Low levels of serum creatinine in maintenance dialysis patients with negligible renal function suggest decreased skeletal muscle mass and/or possible a reduced dietary protein intake and may be associated with increased mortality in dialysis patients. A study of 250 haemodialysis and 140 peritoneal dialysis patients showed that a low level of serum creatinine was an independent predictor of mortality (Avram et al., 1995). The DOPPS study also found higher mortality risk for lower baseline serum creatinine (Pifer et al., 2002). Serum creatinine as nutritional marker was found to be a good predictor of mortality in the HEMO Study (average mortality reduction of 13% per 1 mg/dl elevation in baseline serum creatinine value). Subjects with low serum creatinine (those <12 mg/dl) had elevated relative risk compared to a group defined as having normal serum creatinine of 12 mg/dl or greater (Dwyer et al., 2005).

1.3.1.11.3. Body mass index and obesity

Body mass index (BMI) is the ratio of weight (kilogram) to height (meter) squared. Obesity is defined as a BMI $\geq$ 30kg/m^2. In the general population obesity is mainly associated with comorbid conditions such as diabetes and hypertension that will increase the cardiovascular mortality (Henegar et al., 2001) and many epidemiologic studies have shown a strong association between obesity and decreased survival especially that due to an increased risk of cardiovascular disease (Lew et al., 1979; Byers 1995).

Haemodialysis patients appear to have a lower BMI than age and sex matched control subjects from the general population (Kopple et al., 1997b; USRDS, 2003). Obesity has generally been associated with improved survival among chronic haemodialysis patients. Many observational studies have shown the inverse association between BMI and mortality in maintenance haemodialysis patients. Among these studies; the Diaphane collaborative study group in France which included over 1500 haemodialysis patients, was one of the first to report on the contradictory observation of reduced mortality with high BMI in dialysis patient (Degoulet et al., 1982). The DOPPS study provided baseline demographic, comorbidity and BMI data on 9714 haemodialysis patients in the US and Europe from 1996 to 2000 and showed a decreased mortality risk with increasing BMI (Leavey et al., 2001). Johansen and colleagues (2004) analyzed retrospective data from 418055 maintenance dialysis patients, who were observed over an average of 2 years follow-up time, and found that high BMI was also associated with a reduced risk of hospitalization and a lower rate of mortality. Kalantar-Zadeh and associates (2004a) found that obesity, including morbid obesity (BMI>35), in 54535 haemodialysis patients was associated with survival advantage. The same inverse weight mortality relation in haemodialysis patients was reported in peritoneal dialysis patients. The Canada and United States of America (CANUSA) study included 680 peritoneal dialysis patients, and showed that a 1% reduction in percentage of lean body mass was associated with a 3% change in the relative risk (RR) of death (CANUSA 1996). Johnson and co-workers (2000) studied BMI in 43 peritoneal patients and found that obesity confers a significant survival advantages.

Chung and colleagues (2000) found a similar association between low BMI and increased mortality in 91 peritoneal dialysis patients.

It has been suggested that BMI confers survival advantages in dialysis patients in presence of inflammation or other severe comorbid illnesses. Others have suggested that it is due to survival bias as CKD patients who survive to reach dialysis are those who have higher BMI, cholesterol levels and systolic blood pressure (see section 1.3.1.9.4)

1.3.1.11.4. Serum Cholesterol

Serum cholesterol was discussed in 1.3.1.8.1.1.3.

1.3.1.11.5 Subjective Global Assessment

The CANUSA study included 680 peritoneal dialysis patients in 14 centers in Canada and the United States to evaluate the association of nutritional status with mortality and hospitalisation. It showed that lower scores of SGA (which indicate poor nutritional status) were associated with poorer outcomes. A 1 unit change in the 7 point SGA scale was associated with 25% increase in the relative risk of death (CANUSA 1996). Based on the results of the CANUSA study the DOQI guidelines recommended that SGA should be performed to measure and monitor nutritional status periodically in dialysis patients (K/DOQI 1997b). Pifer and collaborates showed that lower scores of SGA together with lower values of other nutritional parameters (serum albumin, serum creatinine, and BMI) were associated with increased mortality in study sample consisted of 7719 haemodialysis patients from U.S faculties enrolled in DOPPS study (Pifer et al., 2002). A cross sectional study which involved 158 haemodialysis patients to evaluate the predictive value of nutritional markers showed that SGA was a significant predictor of mortality (Hung et al., 2005).

1.3.1.12 Late Referral to Nephrologist

One of factors that may significantly affect morbidity and mortality in dialysis patients is the timing and the quality of care before the start of dialysis. Previous

studies had defined late referral as a patient being seen by nephrologists less than one month (Campbell et al., 1998), four months (Kinchen et al., 2002), or six months (Jungers et al., 2001), before the initiation of dialysis. Late referral can be associated with many adverse effects that may increase patients morbidity and mortality; including hypoalbuminaemia and renal bone disease (Arora et al., 1999; Ifudu et al., 1996), higher rates of emergency dialysis with use of temporary access that is associated with high risk of infection (Schmidt et al., 1998; Ifudu et al 1998), reduced chances of receiving a kidney transplant (Schmidt et al., 1998), increased health care costs (Campbell et al., 1998), and longer hospitalisation (Jungers et al., 1993).

An increasing number of studies, although all observational and retrospective, suggest that patients referred late to a nephrologists for predialysis medical care, compared with those referred early in the disease course, have an enhanced mortality risk once dialysis is initiated. Ratcliffe and coworkers (1984) highlighted the need to refer patients earlier and demonstrated the adverse effect of late referral as they found an association between the length of regular nephrological review and survival after starting RRT. Innes and colleagues (1992) found that early death of patients receiving RRT was associated with late referral to a nephrologist. In this study, the patients who died were first seen by a nephrologist later (a medium of 36 days before starting dialysis) than the age and sex matched subjects who survived (median 30 months) (Innes et al., 1992). Chandna and collaborators (1999) by looking at factors affecting survival and morbidity in 292 dialysis patients showed that late referral for dialysis was a major determinant of poor survival (Chandna et al., 1999). A retrospective national cohort study, using data from the Australia and New Zealand Dialysis and Transplant Registry database (ANZDATA), which included 4243 who patients started dialysis between 1995 and 1998, found that 1141 patients were referred late (27%) (those who needed to commence dialysis within three months of referral to a nephrologist). The median age for both referred early and referred late patients was 56 years with 60% male. Glomerulonephritis constitutes about 30% vs. 34% of patients who were referred early or late, respectively. The percentage of patients with no comorbid condition was 40% vs. 35% and diabetes presented in

28% vs. 35% of those referred early and late, respectively. This study found that late referral is associated with increased mortality, and the authors suggested that early referral to improve predialysis care might improve long term survival. The high incidence of late referral could be related to inadequate communication of primary care doctors with nephrologists (Cass et al., 2002).

1.3.1.13 Health Related Quality of Life

Health related quality of life (HRQoL) refers to the measurement of patient functional wellbeing and general health perception in each of 3 domains: physical, mental, and social. HRQoL may be affected by the clinical manifestation of diseases, the side effects of treatments, and the quality of the relationships of the patients with family members (Valderrabano et al., 2001).

Analysis of data from the DOPPS study showed that lower scores of the 3 components of the health related quality of life short form (physical, mental and kidney disease) were strongly associated with higher risk of death and hospitalization in haemodialysis patients (Mapes et al., 2003). A study of 1000 haemodialysis patients also reported an association between lower scores in physical component summary of quality of life and higher risk of death and hospitalisation (DeOreo, 1997). Lopes and colleagues (2002) showed that mental component summary of quality of life was a significant predictor of death and hospitalisation.

The assessment of HRQoL has become a vital tool in the monitoring of treatment outcomes in patients on various modalities of renal replacement therapy and the influence on morbidity and mortality (Knight et al., 2003; Rosas et al., 2003; and Mapes et al., 2003). Both Karnofsky Performance Status Scale (KPSS) and Short Form-36 Health Survey (SF-36) instruments have been used in assessment of HRQoL in chronic renal failure patients on various treatment modalities, each with it is specific advantages and disadvantages but with generally good correlation (Gokal et al., 1999).

The Karnofsky Performance Status Scale (KPSS) is a physician rating scale designed in 1948 by David Karnofsky, evaluating the performance status of cancer patients. It utilises a single numerical scale that guarantees an objective assessment of the patient's clinical state (Karnofsky et al., 1949). KPSS is perhaps the most commonly used HRQoL instrument. KPSS ranges from 0 (at death) to 100 (that implies full functional capability to carry out normal daily activities without clinical evidence of disease) (Karnofsky et al., 1949; and Evans et al., 1985). KPSS rating is based on observations of a patient's ability to perform common tasks. It is often used in clinical research to monitor and record the health of patients. So Karnofsky score is a method which measures patient performance of activities of daily living.

100	Normal, no complaints or evidence of disease
90	Able to perform normal activity; minor signs and symptoms of disease
80	Able to perform normal activity with effort: some signs and symptoms of disease
70	Cares for self, unable to perform normal activity or to do active work
60	Requires occasional assistance but is able to care for most of own needs
50	Requires considerable assistance and frequent medical care
40	Requires special care and assistance; disabled
30	Hospitalization indicated, although death not imminent; severely disabled
20	Hospitalization necessary; active supportive treatment required, very sick
10	Fatal processes progressing rapidly; moribund
0	Dead

Table.1.5; Karnofsky Functional score

KPSS illustrated in the table above can categorize the patient into 3 groups

1. Patients with ≤ 40 are dependent or requiring institutional or hospital care
2. Patients with 50-70 score require assistance
3. Patients with$\geq$80 are able to carry out normal activity

The short form 36 health survey (SF-36) looks at quality of life as a multidimensional model assessing eight different perspective of HRQoL namely physical functioning; role of limitations due to physical health problems; bodily pain; general health; vitality (energy fatigue); social functioning; role of limitations due to emotional problems; and mental health, which implies psychological distress and psychological well-being (Ware et al., 1993). It unitizes a 36-item questionnaire, which was constructed as an improvement on the older SF-8 and SF-20 scales (Evans et al., 1985). The SF-36 rating is dependent on the patient's assessment perception of their health status, it is high comprehensiveness and conciseness, and it is validity have been variously demonstrated even in different languages (Rebollo et al., 2000; and Kusztal et al., 2003).

1.3.2 Risk factors related to dialysis procedure

1.3.2.1 Dialysis adequacy

The dose of haemodialysis is usually measured in terms of Kt/V for urea or urea reduction ratio (URR). These two measures are calculated from the fractional reduction of blood urea nitrogen concentration during a single haemodialysis treatment (K/DOQI 1997c) and they are practically and mathematically similar (Lowrie et al., 1991). The DOQI Clinical Practice Guidelines (2001) recommended a minimum delivered dose per session be a Kt/V of 1.2 or a URR of 65% for thrice weekly haemodialysis. To achieve these targets, it was further recommended that the prescribed dialysis dose be a Kt/V of 1.3 or a URR of 70%. The recommendation of the DOQI guidelines was based on retrospective studies of mortality outcome for ESRD patients suggested that death progressively increases when URR fall below 60-65% (Hakim et al., 1992; Owen et al., 1993; Held et al., 1996; Lowrie, 1996). The European Best Practice (2002) recommended a higher value than DOQI with Kt/V of 1.4. The UK Renal Association recommended the same dose as the DOQI guidelines.

Low urea clearance on haemodialysis is strongly associated with lower overall survival. The National Cooperative Dialysis study (NCDS) (1983) was the first multicenter randomized control trial to investigate the impact of dialysis dose on

patient outcome and used the concentration of urea in the blood (BUN) as a measure of dialysis dose with lower average BUN indicating a higher dialysis dose. The study included 160 patients using low permeability dialysis membrane who were randomized to different treatment times (2.5-3.5 versus 4.5-5h) and different urea time averaged concentration (TAC) (100 versus 50mg/dl) with a follow up period of more than 6 months. It concluded that patient morbidity and treatment failure are related to the dialysis dose. In a secondary analysis of NCDS data by Gotch and Sargent (1985) were first to propose a quantification of dialysis dose using Kt/V, and showed no further benefits for Kt/V>0.9 with average treatment consisting of dialysis for 4 hours with dialyzer efficiency about one half to one third of modern dialyzers. Another analysis of NCDS by Keshaviah (1993) showed a progressive benefit as Kt/V increased beyond 0.9.

A number of observations are compatible with the hypothesis that more intensive dialysis leads to improved survival. In many reports Kt/V values have increased over the last decade because of concerns about underdialysis and the outcomes compared to those observed previously. Increasing the mean Kt/V from 0.82 (pre-1988) to 1.33 reduced the gross mortality rate from 22.8 down to 9.1% per year (Collins et al., 1994). This was associated with increases in protein catabolic rate from 0.83 to 1.0 and plasma albumin concentration from 35 to 39 g/l. Thus, enhanced nutrition probably contributed to the improvement in survival. In another report, increasing the mean Kt/V from 1.18 to 1.46 (and the URR from 61 to 70%) was associated with reduction in the gross mortality rate from 22.5 to 18.1% per year (Parker et al., 1994). This improvement was achieved with standard cellulose biocompatible membranes. Held and coworkers (1996) analyzed 2311 patients from 374 dialysis centers in the US and showed the risk of mortality was 7% lower with 0.1% increase in Kt/V. The DOPPS study observed that mortality and morbidity decrease with increasing Kt/V to at least 1.4 (McCullough et al., 2000). Port and colleagues (2002) included 45967 haemodialysis patients and found that a higher dialysis dose substantially above the DOQI guidelines was a strong predictor of lower patient mortality for patients of all body sizes. All of the above studies were, however, observational in nature.

However, in the HEMO study, a large prospective clinical trial, 1846 patients were randomly assigned to a standard or high dose of dialysis and a low or high flux dialyzer, and produced surprising and disappointing results to those who believe in improving the patient outcomes with higher dialysis dose than those recommended by guidelines (Eknoyan et al., 2002). The standard dose goal was an equilibrated Kt/V of 1.05, which is equivalent to a single pool Kt/V of 1.25 or URR of 65%. The high dose goal was an equilibrated Kt/V of 1.45, equivalent to a single pool Kt/V 1.65 or a URR 75%. the primary outcome was death from any cause, while the main secondary outcomes were rate of all hospitalisations (but excluding those related to access), and the composite outcomes of the first hospitalisation for cardiac problem or death from any cause, the first hospitalisation for an infectious cause or death, and the first decline of greater than 15% of the serum albumin from baseline value or death. The following results concerning dialysis dose were reported at a mean follow up of 4.5 years:

- The primary outcomes for the HEMO study demonstrated no significant differences in all cause mortality between patients treated in the standard dose versus high dose groups, between the low flux and high flux dialyzer groups.
- The risk of the main secondary outcomes was also the same for both dialysis doses. However, there was a 20% reduction in cardiac deaths in the high flux group (but not all cause mortality).

The HEMO study has drawn a line under the adequacy debate as it confirmed that 3 times/week therapy will remain the standard treatment for the majority. The results of the HEMO study were disappointing, to many nephrologists who believed that an increase in the dose of haemodialysis, and the use of high flux membranes, could benefit patient survival. This opinion based was mainly on the results of observational studies.

1.3.2.2 Dialysis time

Several studies have documented a relationship between shorter dialysis time and poorer outcome (Held et al., 1991; and Woods et al., 1996). Patients dialyzed fewer than 3.5 hours three times per week have approximately twice the mortality risk compared to patients dialyzed 4 or more hours three times per week (Held et al., 1991). A study from the Tassin group from France, which included 445 haemodialysis patients, has reported one of the best dialysis survival estimates of any program. They have shown that patients receiving large dose of dialysis with Kt/V of 1.67 (8 hours per session, 3 times/week), had survival rate of (87% at 5 years, 65% at 15 years and 43% at 20 years). Ninety eight percent of these patients achieved normotension without the need for antihypertensive medications (Charra et al., 1992; and 2004).

Short daily haemodialysis is an emerging and promising therapy that may prove not only to improve patient outcomes, but to provide a cost-effective alternative to conventional in-centre haemodialysis. Several observational studies have evaluated the potential benefits and risks of daily haemodialysis, compared with intermittent haemodialysis. Short daily haemodialysis is associated with improved patients survival, nutritional status, quality of life and blood pressure control, reduced left ventricular hypertrophy, and reduction in cardiovascular risk (Wood et al., 1999; Maduell et al., 2003; Chan et al., 2003). These effects seem to be related to an optimization of body volume status. Future studies in this area will hopefully help established a role for daily haemodialysis in the next decade. Unfortunately these observational studies suffer from several methodological limitations, including small sample size, use of non ideal control groups and selection bias (Suri et al., 2006). More explanation about effect of dialysis time will hopefully come up from a randomized control trial currently started in Canada. It will examine the impact of nocturnal haemodialysis compared to conventional haemodialysis on the clinical outcomes for a six months period. The primary outcome is change in left ventricular mass. The secondary outcomes include blood pressure control, mineral metabolism, anaemia, HRQoL and costs) (Walsh et al., 2006).

1.3.2.3. Haemodialysis membrane

Survival, dialysis adequacy and the biocompatibility of haemodialysis membrane may all be closely interrelated. A report from the USRDS case mix adequacy study enrolled 2410 haemodialysis patients. The types of dialysis membranes used were broadly classified into three categories: un-substituted cellulose, modified cellulose (generally cellulose membranes that have been modified by substitutions of some or most of their hydroxyl moieties) and synthetic membranes that are not cellulose based. The results showed that the relative risk of mortality of patients dialyzed with modified cellulose or synthetic membranes was at least 20% less than that of patients treated with un-substituted cellulose membranes, this study suggest that the dialysis membrane plays an important role in the outcome of haemodialysis patients (Hakim et al., 1996). One possible contributing factor to this difference other than biocompatibility was that either modified cellulose or synthetic membranes typically have higher surface areas and higher urea clearances than un-substituted cellulose membranes and patients dialyzed with modified or synthetic membranes received significantly more intensive dialysis than those dialyzed with cellulose membranes (Kt/V of 1.14 versus 1.07).

Further information regarding the effect of dialysis membrane on survival came from the HEMO study that failed to show any survival advantages of increasing neither dialysis dose nor the type of dialysis membrane. There was no significant difference in the all cause of death between high and low flux groups (RR of 0.92). But in the high flux group, there was a significant reduction in the risk of first hospitalisation and death from a cardiac cause (but not all cause mortality) compared with low flux group (Eknoyan et al., 2002). Further clarification about importance of membrane flux will hopefully arise from the Membrane Permeability Outcome (MPO) study currently underway in Europe. This randomized control trial, which included only incident patients, will examine the influence of high flux membranes on clinical outcomes (including mortality, morbidity, vascular access survival and nutritional status) (Locatelli et al 2005).

1.3.2.4. Vascular Access

There are three types of vascular access (native arteriovenous fistula (AVF) constructed by anastomosis of native artery with a native vein, synthetic Arteriovenous fistula/graft (AVG), and central venous catheter (CVC) (cuffed, tunnelled internal jugular dialysis catheter). The difference between these types has been demonstrated by DOPPS study which showed that AVF is the most desirable vascular access for haemodialysis because AVF produces the highest flows, minimizes infection and has the greatest longevity (Rayner et al., 2003). New AVF should be allowed to mature for at least 1 month, and ideally for 3 to 4 months, prior to an anticipated need for haemodialysis (K/DOQI 1997d). This avoids the need for emergency insertion of central venous catheter, which is associated with morbidity due to major vessel thrombosis and infection (Dhingra et al., 2001).

Haemodialysis access failure remains a major source of morbidity and hospitalisation for ESRD patients. Access failure is second only to cardiovascular disease as a cause of hospitalisation (Eggers 2004). Infection is the second leading cause of death in dialysis patients and vascular access especially venous catheters are associated with increased risk of infection related mortality among haemodialysis patients. Moreover, the venous catheter for haemodialysis is associated with increased risk of thrombosis, central venous stenosis, short access survival and inadequate dialysis (Feldman et al., 1996; Nassar et al., 2001). The USRDS (1996) reported that cardiac deaths accounted for 45% of total deaths and also showed the associated risk of death due to cardiac cause was higher among patients dialyzed with CVC when compared with AVG and AVF. The risk of septicaemia associated with venous catheters is elevated in haemodialysis patients. Avoiding temporary vascular access may decrease the incidence of septicaemia and mortality associated with haemodialysis (Powe et al., 1999).

1.3.2.5 Modality of dialysis

Comparison between modalities is difficult because mortality difference between haemodialysis and peritoneal dialysis may be due to the difference in patient selection and characteristics between prevalent and incident ESRD patients

(Friedman 2000). For instance, the patients selected to peritoneal dialysis tend to be younger and less likely to have CVD and other comorbid conditions compared with haemodialysis patients (Thamer et al., 2000; Stack 2002).

An observational study of 822 Canadian dialysis patients comparing the mortality differences between haemodialysis and peritoneal dialysis found that both modalities are associated with similar overall survival rates when comorbidity was taken in account because haemodialysis patients had higher burden of comorbid illness and acute onset of renal failure compared with peritoneal dialysis patients (Murphy et al., 2000). Studies in mortality comparison of peritoneal dialysis and haemodialysis among new ESRD patients has suggested that survival on peritoneal dialysis is at least similar to that of haemodialysis, if not better within the first 2 years of therapy (Gokal et al., 1999; Collins et al., 1999; Tanna et al., 2000). Efforts should be made to start and complete adequately powered randomized control trials to compare peritoneal dialysis and haemodialysis modalities which would ensure that any differences in outcomes seen on follow up would be solely due to one modality treatment or the other.

1.3.2.6 Vintage

Vintage is length of time on dialysis. Prolonged dialysis is a significant predictor of death in chronic haemodialysis patients (Iseki et al 2003). Chertow and associates (2000) found that the mortality risk increases by 6% with each year on dialysis therapy. UKRR and USRDS demonstrated a rising hazard of death with increasing length of time on RRT. Vintage is important also for patients undergoing kidney transplant, as Cosio and colleagues (1998) showed that pre-transplant dialysis has a significant effect on patient survival after transplantation. Increased time on dialysis prior to renal transplantation was associated with decreased patient survival. They explained this by the development of heart disease in long term dialysis patients.

1.4. Aim of the Study

The studies described in this thesis were devised with the following aims:

- To evaluate the importance of using subjective global assessment (SGA) alone in predicting the survival and whether it is valuable to have SGA assessed to improve prediction of haemodialysis patients' outcome.
- To assess the impact of comorbid illness and nutritional status upon dialysis patient survival.
- To investigate the factors that predicting the survival of all patients starting RRT in Southeast Scotland in 2003 and 2004.
- To compare the data of this study with the data of the study previously obtained to predict the survival of dialysis patients in Edinburgh in 2001.

Chapter 2

Methods

2.1. Introduction

This study was conducted in the renal unit of Edinburgh Royal Infirmary (RIE) that provides a renal service for the population of the Lothian and Borders region, about 850000 people. In 2003 the renal unit moved to the new Royal infirmary site at little France. The UKRR ninth annual report 2006 showed that Edinburgh renal unit cared for 273 haemodialysis patients, 61 peritoneal dialysis patients and 372 transplant patients.

In this chapter I will describe the methods used in an incident cohort Edinburgh study that included patients who started RRT in 2003 and 2004 and a cross-sectional study of prevalent patients which examined the additional predictive value of subjective global assessment (SGA) on survival of dialysis patients.

2.2. Patients

2.2.1. Incident Cohort Edinburgh Study

Patients starting RRT for end stage renal disease (ESRD) at the RIE renal unit between 01/01/2003 and 31/12/2004 were included. Patients with acute renal failure were excluded. Data collection for 183 patients (85 patients started RRT in 2003 and 98 patients in 2004) enrolled in this study was started at 11/10/2005. 156 patients started on haemodialysis, 25 patients started on peritoneal dialysis and only 2 patients started as pre-emptive kidney transplant. 13 patients died within the first 90 days of their treatment. This study was a continuation of auditing thus ethical approval was not required.

2.2.2. Prevalent Cross-Sectional Study

This study was initiated by a team of dieticians in the renal unit aiming to find a malnutrition screening tool for dialysis patients that could save dietician, nursing and medical staff time. This study included 122 prevalent dialysis out-patients at the RIE (13 peritoneal dialysis and 109 haemodialysis). The subjective global assessment [will be described later in this chapter] was measured by dieticians in the renal unit for all patients by taking the history and measuring body weight needed to provide the score from 1 to 7 **(Appendix 4)**. Follow up of the dietician study was started in

11/4/2005 and continued until 12/4/2007 (period of 2 years). The ethical approval was granted for the study to the dietician team.

2.3. Data collection

2.3.1. Incident cohort study

The data were collected by one observer (FL) throughout, to avoid inter observer errors in scoring of patients. At the beginning the data was collected from computer based information (Proton) and then by interrogation of patients' clinical notes to extract information on comorbidity and complete the data that was uncertain or missing from the Proton database.

Survival data was obtained at January 2007 and analyzed in 2 different ways:-

I. In the continual survival study (chapter 5) patients were followed until 1/1/2007 a period of minimum 2 years for who started RRT in December 2004 and maximum 4 years for those who started RRT in January 2003 or until death if sooner.
II. In the comparison survival study (chapter 6) all patients were followed for a period of exactly 2 years (minimum 7 days and maximum 730 days) unless the patients died.

The hospitalisation data was collected by using the patients' admission system (PAS) to determine the total period of hospital admission for all patients within exact 2 years since they started their RRT.

2.3.2. Prevalent cross section study

The dietician team collected the following data age, gender, laboratory (urea, albumin, CRP, Cholesterol), nutritional measurements [(body mass index (BMI), mid arm circumference (MAMC), and triceps skin fold (TSF)], and total SGA score). The study was supplemented by collecting comorbidity from the patients' notes, and primary renal diagnosis and cause of death based on ERA-EDTA codes. Survival data was obtained at April 2007 (for a period of exact 2 years). Hospitalization was

studied by assessing the frequency of hospitalisation and its total duration in days over the 2 years of the study.

2.4. The data set

The main reason of choosing these data sets was to define a minimum data set providing maximal information that will help in evaluating patient survival.

1. Data which give a very clear description of the Lothian and Borders dialysis population in terms of demography; primary renal disease; and the burden of comorbid disease.
2. Data which could describe how patients' initial therapy was conducted, and how long they had been known to the renal unit before starting dialysis in 2 different periods 3 and 6 months.
3. Data which would be most useful in predicting patient survival.
4. Data which provides information about the nutritional status.

2.5. Baseline data

2.5.1. Incident cohort study

- Date- of birth, of start of the study, of end of the study, of starting of treatment, of death. Demographic (age, and gender), according to UKRR patients were grouped into 2 age groups (young <65, and old ≥65 years) to determine the effect of age on patients survival.

- Clinical (the first mode of RRT, access for first RRT, primary renal diagnosis, causes of death and comorbid conditions). Permanent access is used to describe an arterio-venous fistula/graft for haemodialysis patients and Tenckhoff catheter for peritoneal dialysis patients. Comorbid conditions were scored using 3 different comorbidity scores (Charlson, Khan, and Davies)

- Biochemical [serum- albumin (g/l), creatinine (μmol/l), urea (mmol/l), haemoglobin (g/l), cholesterol (mmol/l), CRP (mg/l), and also estimated GFR

(ml/min)] all these laboratory data were collected at zero time or when patient started RRT.

- Referral to nephrology care unit or the length of follow-up by a nephrologist prior to commencing RRT was determined by calculating the difference between the date of the first biochemical investigations recorded on Proton and the date of the first RRT session. Referral times of 90 days or more from start of RRT were considered as early referral. Referral times less than 90 days from start of RRT were defined as late referral. Another consideration in the same way was done for a period of 6 month

2.5.2. Prevalent cross section study

- Date- of birth, Start of the study, end of the study in, starting of treatment, of death. Demographic (age, and gender).
- Clinical (mode of RRT at start of the study, duration of treatment since the patients started RRT, primary renal diagnosis, comorbid conditions, statin therapy, and causes of death). Comorbid conditions were scored using Khan score.

- Biochemical [serum- albumin (g/l), urea (mmol/l), cholesterol (μmol/l), and CRP (mg/l)] all these laboratory data were collected at time of the study started.

- Nutritional measurements (body mass index (BMI), mid arm muscle circumference (MAMC), triceps skin fold (TSF), and subjective global assessment (SGA)). These measurements have been assessed by renal dieticians.

2.6. Outcome variables

2.6.1. Vintage

Vintage is the time spent on RRT which was calculated differently in both studies as explained below.

- In the incident cohort study duration of treatment has been calculated in days as the time difference between date of starting dialysis and either the date of end of study follow-up or date of death.
    I. In the continual survival study (chapter 5) the period calculated of minimum 2 years for who started RRT in December 2004 and maximum 4 years for who started RRT in January 2003 unless the patients died. The median time of treatment (median time of follow up) was 817 days (minimum 7 days and maximum 1440 days).
    II. In the comparison study (chapter 6) the calculated period of exactly 2 years (minimum 7 days and maximum 730 days) unless the patients died.

- In the prevalent cross sectional study the time spent on treatment has been calculated in days as the time difference between date of starting the study and either the date of end of study follow-up or date of death.

2.6.2. Hospitalisation

Hospitalisation is the percentage of patients live time spent in hospital. Hospitalisation was defined as any hospital admission that included at least one overnight stay in the hospital. The admission day was counted as one full hospitalisation day but the discharge day was not. Therefore, the minimum duration of hospitalisation per admission was 1 day. Percentage of hospitalisation was the sum of all hospital admissions as a percentage of the sum of total duration of treatment.

- In the incident study the data on hospital admission were collected for exactly 2 years from the date of starting RRT or until the patient died.
- In the prevalent study the data on hospital admission were collected for exactly 2 years from the date of starting the study until the end of the study or until the patient died.

2.6.3. Death

The date of death was recorded to calculate the duration of survival for those who died in the study. Causes of death were coded according to ERA-EDTA as shown in section 2.10. The data for cause of death was extracted from Proton database.

2.7. Instruments of data collection, coding and grouping

I. Primary renal diagnosis codes and grouping based on ERA-EDTA classification was used in all studies

II. Cause of death codes and grouping according to ERA-EDTA classification was used in all studies

III. Comorbidity

- □. In the incident cohort continual study Charlson index, Khan score and Davies score were all used in the analysis
- □. In the incident comparison study; patients were stratified into three risk groups according to age and number of comorbid condition which is similar to Khan's method but with fewer comorbid conditions (CCF, CPD, Liver disease)
- □. In the prevalent cross section study only the Khan score used.

IV. SGA classification was used only in prevalent cross section study

2.8. Comorbid diseases

20 different comorbid diseases listed below have been collected which allow any kind of comorbidity score to be used to assess the comorbidity burden. In the incident study the comorbid diseases were assessed at the time when patients started RRT, but in the prevalent cross sectional study comorbid illnesses were collected at the start of the study. All the detailed information about comorbidity was audited from the patients clinical notes and assessed by using 3 different scores:-

(I) The Charlson index (CCI) that includes more conditions than Khan and Davies scores. Angina was considered as single comorbid illness (**Appendix 1.1**). Charlson scores ranges from 0 to 35 and according to total score patients were assigned into one of following 4 groups which roughly represented quartiles.

- Group 0 = patients with no comorbid conditions (CCI = 0)
- Group 1 = patients with one comorbid condition (CCI = 1)
- Group 2 = patients with two comorbid conditions (CCI = 2)
- Group 3 = patients with more than two comorbid conditions (CCI > 2)

(II) The Khan score includes age and total comorbid conditions to form classify patients into 3 risk groups (low, moderate and high) **(Appendix 1.2)**.

(III) The Davies score consists of seven comorbid conditions and age is not included **(Appendix 1.3)**. Similar to Charlson scores the Davies scores were separated into 4 groups which roughly represented quartiles.

- Group 0 = patients with no comorbid conditions (Davies = 0)
- Group 1 = patients with one comorbid condition (Davies = 1)
- Group 2 = patients with two comorbid conditions (Davies = 2)
- Group 3 = patients with more than two comorbid conditions (Davies > 2)

The 3 scores had calculated their total score from the following comorbid conditions:-

1. Myocardial infarction (MI) (raised cardiac enzymes, ECG changes, PTCA/CABG)
2. Angina (chest pain relieved by nitroglycerine, or positive exercise test)
3. Cerebrovascular (CeVD) [(transit ischaemic attack (TIA), cerebrovascular accident (CVA)].
4. Congestive cardiac failure (CCF) was difficult to assess. Therefore, we used the Scottish Renal Registry criteria in defining CCF **(Appendix 5)**
5. Peripheral vascular disease (PVD) (intermittent claudication, amputation, PV bypass)
6. Chronic pulmonary disease (CPD) (chronic obstructive airway disease (COAD), Asthma, pulmonary fibrosis)
7. Connective tissue disease (Rheumatoid arthritis, SLE, Systemic sclerosis)
8. Mild liver diseases (hepatitis or elevated liver enzymes).

9. Severe liver disease (liver cirrhosis or portal hypertension) which scores higher in CCI
10. Diabetes mellitus (DM)
11. Diabetes mellitus with end organ damage such as peripheral neuropathy, retinopathy and autonomic complications scored higher in CCI
12. Peptic ulcer disease
13. Dementia
14. Hemiplegia
15. Non Metastatic tumours (skin tumours not included)
16. Lymphoma
17. Leukaemia
18. Multiple myeloma.
19. HIV
20. Metastatic solid Tumour, CCI (skin tumours not included) has the highest score in CCI.

2.9. Primary renal diagnosis

The primary renal diagnosis codes were chosen from the list issued by European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) **(Appendix 2)**. Diagnosis in ERA-EDTA list has previously been classified into 5 categories:

(1) Glomerulonephritis

(2) Interstitial nephritis

(3) Multisystem diseases

(4) Diabetes

(5) Unknown causes

2.10. Causes of death

The death cause codes were chosen from the list issued by ERA-EDTA **(Appendix 3)** that has been classified in main 5 groups

(1) Cardiovascular/vascular causes

(2) Infection

(3) Malignancy

(4) Unknown causes

(5) Other known causes

2.11. Subjective Global Assessment

Subjective global assessment (SGA) is a malnutrition screening tool that identifies abnormal nutritional status in dialysis patients based on these following 4 items:

1. Weight changes over the past 6 months. A loss of >10% is severe and 5% to 10% is moderate, while 0-5% is mild.
2. Dietary intake assessed by comparison of the patient's usual and recommended intake to current intake. Duration and frequency of gastrointestinal (GIT) symptoms (anorexia, nausea, vomiting and diarrhoea) are also assessed.
3. Loss of subcutaneous fat by examining the fat pads directly below the eyes and by gently pinching the skin above the triceps and biceps. The fat pads should appear as a slight bulge in a normally nourished person but are "hollow" in a malnourished person.
4. Muscle wasting or presence of ankle, sacral oedema and ascites. Muscle wasting can be assessed by examining the temporalis muscle, the prominence of the clavicles, the contour of the shoulders (rounded indicates well-nourished; squared indicates malnutrition).

For each above item a score on a 7 point scale is recorded with higher score indicating better nutritional status. The score from each of the 4 items are averaged to give the SGA rating which ranges from 1=severely malnourished to 7= normal nutrition. Patients are categorized into 3 distinct classes of nutritional status, well nourished (SGA A), moderately malnourished (SGA B), and severely malnourished (SGA C) (**Table 2.1**).

The SGA, being a subjective method, relies on the observer's ability to collect and interpret information, and as a result, is likely to suffer from observer bias. This bias, however, was minimized by restricting the use of the SGA to well-trained dieticians

with an expertise in the use of this clinical instrument and they work together to ensure consistency. Also the measured data (MAMC, TSF and body weight) were carried 3 times and the average was recorded as the value for these parameters.

SGA Classification						
severe		moderate	mild		normal	
1	2	3	4	5	6	7
C		**B**			**A**	

Table 2.1; Classification of subjective global assessment

2.12. Statistical analysis

Data management, computations and graphical representations were performed using the standard Statistical Package for Social Sciences software (SPSS for Windows, Version 14.0, SPSS Inc., Chicago, IL, USA), and Microsoft Excel. Data were tested for the symmetry of its distribution, when the skewness value was less than one, the variable was considered normally distributed.

When the variables were normally distributed, continuous variables were expressed as mean ± standard deviation (SD) and compared with parametric tests (independent sample t-test when comparisons between groups were made). When the variables were skewed, continuous variables were expressed as median and interquartile range (IQR) and/or minimum and maximum values and compared with nonparametric tests (Mann-Whitney U test when comparison between groups were made). Categorical variables were expressed as proportions and compared with the Chi-square test (χ^2 test).

The overall median percentage of live time spent in hospital and median percentage between different groups was estimated using nonparametric Kruskal Wallis test.

The associations between the different continuous variables were performed using Pearson's rank correlation coefficient.

The P values for comparison of survival curves were determined by the log-rank test by using Kaplan-Meier model. A multivariate time-to-death adjusted Cox regression model was used to identify time-independent predictors of cumulative risk of death. A forwards likelihood-ratio selection procedure was applied (inclusion criterion $P \leq 0.05$, exclusion criterion $P \geq 0.055$) to test for their independent contribution to predict survival within the model, the relative risk (RR) and their 95% confidence intervals (95% CI) were calculated. Survival time was measured in terms of number of days until death or censorship exactly 730 days in the prevalent cross section study and the incident comparison study but minimum 7 days and maximum 1440 days in the incident continual study.

Chapter 3

Pilot study

3.1. Introduction

Comorbid conditions are difficult to collect from clinical note as it is time consuming. However, relying on computer based information may not be enough to provide comprehensive details of comorbid conditions.

3.2. Aim

To find whether collecting information about comorbidity from the computer based data system (Proton) was adequate or it would be necessary to collect the information about comorbidity from the clinical notes.

3.3. Method

30 patients randomly selected out of all incident patients started dialysis in 2003. The 20 comorbid illnesses considered for this study as listed in chapter 2 were recorded from both the computer based data system (Proton) and from the clinical notes of the same patients. The comorbid conditions information from computer and clinical note were compared to see whether both sources were equivalent or not in providing information on comorbidity.

3.4. Results

Table 3.1 shows several comorbid conditions were not recorded on computer based system, following the criteria explained in chapter 2 and appendix 5 in definition of comorbid condition. Congestive cardiac failure was the most difficult comorbidity to assess and it was rarely clearly mentioned on Proton. In addition, the label ischaemic heart disease was often used on Proton. However, angina and myocardial infarction are different comorbid illnesses according to Charlson, Khan and Davies comorbidity scores.

Furthermore, the Charlson index (explained in chapter 2) was used to classify the patients into 4 risk groups according to the total Charlson comorbidity Index (CCI), the patients who scored from 3 to 7 on the total Charlson index were gathered into a CCI>2 group, whereas the other groups were given a score equivalent to the total

CCI score. The risk groups produced from the information collected from Proton were compared with risk groups of clinical notes. The percentage of patient with no comorbid conditions on Proton dropped after auditing the clinical notes (36.7% vs. 23.3%). On the other hand the number of patients with 2 and >2 comorbid conditions increased when the comorbid conditions were collected from the clinical notes (Table 3.1).

Groups of Charlson score	**Proton**		**Clinical notes**	
	no	**%**	**no**	**%**
CCI = 0	11	36.7	7	23.3
CCI = 1	6	20	4	13.3
CCI = 2	4	13.3	8	26.7
CCI > 2	9	30	11	36.7
Total number of patients	30	100	30	100

Table 3.1: Comorbidity differences between Proton and clinical notes

3.5. Conclusion

The study showed that computer based data did not include all the information needed for this work and it is better to extract the comorbid information from the clinical note. A clear definition for congestive cardiac failure and ischaemic heart disease should be considered in recording comorbid diseases on proton.

Chapter 4

Survival Analysis of the Prevalent Cross Section Study

4.1. Abstract

Introduction

Subjective global assessment (SGA), which assesses nutritional status based on features of the history and physical examination, can be used to estimate malnutrition in dialysis patients, and has been shown to be predictive of poor outcomes.

Aims

A prospective study of 122 prevalent dialysis patients was originally designed to determine whether the SGA provided added value on top of more simply collected numerical and diagnostic data.

Method

SGA was performed by an observer unaware of the results of the objective measurements at the beginning of the study. Numerical data including serum albumin, urea, body mass index (BMI), mid arm muscle circumference (MAMC), serum cholesterol, and C-reactive protein (CRP) were extracted from the renal IT system, and comorbidity was determined from case records and scored using the Khan method. Univariate and multivariate Cox regression was used to identify independent predictors of survival.

Results

At 24 months 87 patients (71.3%) were alive. Cardiovascular disease was the leading cause of death (57.1%). A univariate analysis showed that SGA was strong predictor of patients outcome (p=0.001), the most severely malnourished patients having 25% survival versus 80.6% for the best scores. The Cox regression model of multivariate analysis showed that patient survival was significantly associated with age, with SGA, CRP, and the presence of comorbid diseases at start of dialysis.

Conclusion

Significant additional information is provided by measuring SGA.

4.2. Introduction

Malnutrition is a common risk factor in dialysis patients and there is no ideal method that can be used to assess malnutrition in these patients. A dietician team initiated a study aiming to find a nutritional screening tool that reduced of dietetic, nursing or medical staff time, with the hypothesis that a computer based malnutrition screening tool could identify dialysis patients at risk of malnutrition as accurately as subjective global assessment (SGA). They had found that SGA, which relies on an experienced dietician carrying out the assessment, was time consuming, meaning that they could not use this method to assess the nutritional status of dialysis patients every 4 months as recommendation by the international guidelines (DOQI 1997). In this study I extended the dieticians original nutritional study by adding the different comorbid conditions at start of the study aiming to evaluate whether there was added value in using SGA to predict patient's survival.

4.3. Methods

This cross section study included 122 prevalent patients receiving dialysis treatment at the renal unit in the RIE, selected by the dieticians in the renal unit according to the following criteria

1. the study involved out-patient dialysis patients only
2. Patients who had been on dialysis for more than 90 days
3. Patients were able to communicate and answer simple questions required for SGA.

SGA assessments includes, patient history of weight loss, incidence of anorexia, and incidence of vomiting, and the physician's grading of muscle wasting, presence of oedema, and loss of subcutaneous fat. On the basis of these assessments, each patient was given a score that reflect the nutritional status **(Chapter 2)**.Other nutritional parameters were measured; BMI, TSF, MAMC, serum albumin, serum urea, and serum cholesterol in addition to age, sex, modality of treatment, primary renal diagnosis (based on ERA-EDTA codes for renal disease), and CRP at the time of start of the study (11/4/2005). Comorbid diseases were collected by one observer (FL). Patients were followed until 12/4/2007 (2 years).

4.4. Patient mortality and causes of death

Figure 4.1 shows the cumulative survival curve in this study and after 2 years of follow up 35 patients (28.7%) had died. Cardiovascular disease accounts for over half of all deaths, while infections account for more than one quarter (**Table 4.1).** List of all causes of death according to ERA-EDTA classification is presented in **Table 4.2.**

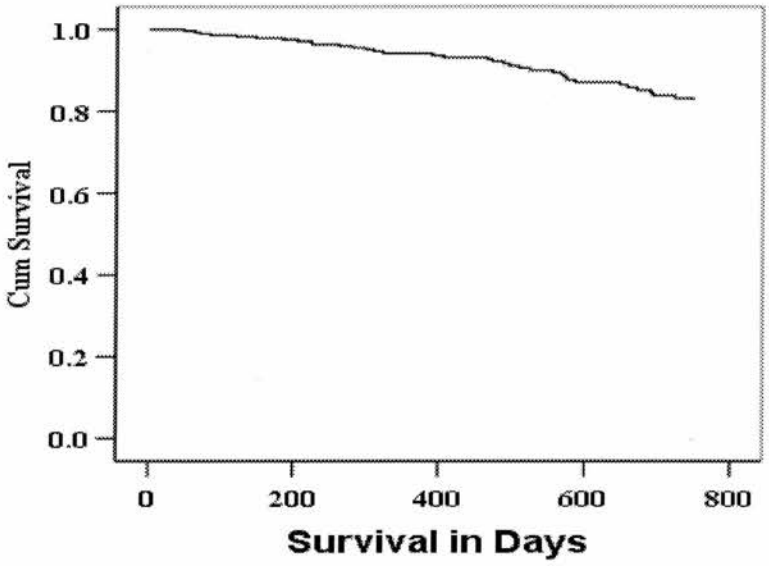

Figure 4.1; Survival curve of prevalent patients

Cause of death	**n**	*%*
Cardiovascular diseases/vascular	20	57.1
Infection	10	28.6
Malignancy	2	5.7
Others	3	8.6

Table 4.1; Causes of death

ERA-EDTA Cause of Death	Code	no	(%)
Cardiovascular/vascular causes			
Cardiac arrest Unknown cause	15	14	(40%)
Myocardial ischemia and infarction	11	4	(11.4%)
Cerebrovascular accident	22	2	(5.7%)
Infection			
Pulmonary infection	31	4	(11.4%)
Septicaemia	35	6	(17.2%)
Malignancy	67	2	(5.7%)
Others			
ESRF treatment withdrawn for medical reasons	54	3	(8.6%)

Table 4.2; List of all causes of death

4.5. Demographic data

The main clinical and demographic characteristics with summary statistics for all 122 prevalent patients are shown in table 4.3 and 4.4 below. Data are presented as mean ± SD, median (range) and number (%). The minimal dialysis time was 282 days as the patients involved in this study were those who survived more than 6 months.

Variables	No	%
Age groups		
< 65 years	68	55.7
≥ 65 years	54	44.3
Gender		
Male	75	61.5
Female	47	38.5
Modality		
Haemodialysis	109	89.3
Peritoneal dialysis	13	10.7
Statin Therapy		
Yes	49	40.1
No	73	59.9

Table 4.3; Basic clinical and demographic characteristics of study

Variables	Median (min-max)	Mean ± SD
Age (years)	60.5 (17-88)	
CRP (mg/l)	8 (3-22)	
BMI (kg/m^2)	25.2 (17.3-46.4)	
Time on RRT Days Years	 1491 (282-14860) 4.1 (0.8-40.7)	
Serum albumin (g/l)		37.8 ± 5.2
Serum urea (mmol/l)		18.7 ± 4.3
Serum cholesterol (mmol/l)		4.2 ± 1.0
MAMC (cm)		24.5 ± 3.4
TSF (mm)		14.9 ± 7.2

Table 4.4; Summary statistics of the study population at entry to the study

4.6. Patient characteristics and univariate analysis

Univariate analysis of the patients showed that age, comorbidity, nutritional status based on SGA classification, primary renal diagnosis, serum urea, serum albumin, serum cholesterol, CRP, and time spent on dialysis prior to the study, were all significantly associated with death. Patients' sex did not significantly influence survival, nor did BMI, MAMC, or modality of treatment **(Table 4.5).**

	Cohort n=122	**Survivors n=87 (71.3%)**	**Dead n=35 (28.7%)**	**p-value & statistic test**
Median age (years) (IQR)	60.5 (46-72)	57 (43-68)	72 (58-76)	P=0.0001 M W
Age≥ 65 years	54 (44.3)	31 (35.6)	23 (65.7%)	p=0.002
Gender				p=0.542 χ^2
Male	75 (61.5)	52 (59.8)	23 (65.7)	
Female	47 (38.5)	35 (40.2)	12 (34.3)	
Modality				p=0.636 χ^2
Haemodialysis	109 (89.3)	77 (88.5)	32 (91.4)	
Peritoneal dialysis	13 (10.7)	10 (11.5)	3 (8.6)	
Statin Therapy				p=0.149 χ^2
Yes	48 (39.3)	30 (34.5)	18 (51.4)	
No	71 (58.2)	45 (62.1)	17 (48.6)	
Diagnosis				p=0.001 χ^2
glomerulonephritis	32 (26.2)	24 (27.6)	8 (22.9)	
Interstitial Nephritis	29 (23.8)	27 (31)	2 (5.7)	
Multisystem disease	25 (20.5)	10 (11.5)	15 (42.9)	
Diabetic nephropathy	7 (5.7)	5 (5.7)	2 (5.7)	
Unknown	29 (23.8)	21(24.1)	8 (22.9)	
SGA				p=0.005 χ^2
Severe	4 (3.3)	1 (1.1)	3 (8.6)	
Moderate	41 (33.6)	24 (27.6)	17 (48.6)	
Normal	77 (63.1)	62 (71.3)	15 (42.9)	
Khan score				p=0.0001 χ^2
Low	43 (35.2)	41 (47.1)	2 (5.7)	
Medium	29 (23.8)	23 (26.4)	6 (17.1)	
High	50 (41)	23 (26.4)	27 (77.1)	
Ischaemic heart disease	42 (34.4)	19 (21.8)	23 (65.7)	p=0.0001 χ^2
Congestive cardiac failure	18 (14.8)	6 (6.9)	12 (34.3)	p=0.0001 χ^2
Peripheral vascular disease	22 (18)	7 (8)	15 (42.9)	p=0.0001 χ^2
Cerebrovascular disease	24 (19.4)	8 (9.2)	16 (45.7)	p=0.0001 χ^2
Diabetes	21 (17.2)	11 (12.6)	10 (28.6)	p=0.035 χ^2
Peptic ulcer disease	8 (6.6)	3 (3.4)	5 (14.3)	p=0.029 χ^2
Chronic pulmonary disease	18 (14.8)	11 (12.6)	7 (20)	p=0.300 χ^2
Malignancy	11 (9)	7 (8)	4 (11.4)	p=0.555 χ^2
Mean Albumin (g/l)	37.8 SD 5.2	38.6 SD 4.1	35.9 SD 4.1	p=0.001 T-test
Mean Urea (mmol/l)	18.7 SD 4.3	19.2 SD 4.3	17.3 SD 4.1	p=0.023 T test
Mean Cholesterol (mmol/l)	4.2 SD 1.0	4.3 SD 1	3.9 SD 0.9	p=0.049 T test
CRP (mg/l) (IQR)	8 (5-21)	6 (5-15)	18 (8-31)	p=0.0001 M-W
Median Time on dialysis (days) & (years) (IQR)	1491 (1020-3222) 4.1 (2.7-8.8)	1753 (1142-3370) 4.8 (3.1-9.2)	1234 (698-2190) 3.3 (1.9-6)	p=0.008 M-W
Median BMI (kg/m^2) (IQR)	25.2 (21.5-28.6)	25.5 (21.6-28.7)	24.2 (20.9-25.9)	p=0.094 M-W
Mean MAMC (cm)	24.5 SD 3.4	24.9 SD 3.4	23.6 SD 3.2	p=0.054 T teat

Table 4.5; Patient characteristics and univariate analysis, χ^2=Chi square test, M.W= Mann Whitney test

4.7. Comparison between the groups, according to survival

4.7.1. Age

In this study the median age of 122 patients was 60.5 years (IQR= 46-72). When these patients were distributed according to age in 10 year periods, 46% were older than 60 years **(Figure 4.2)**.

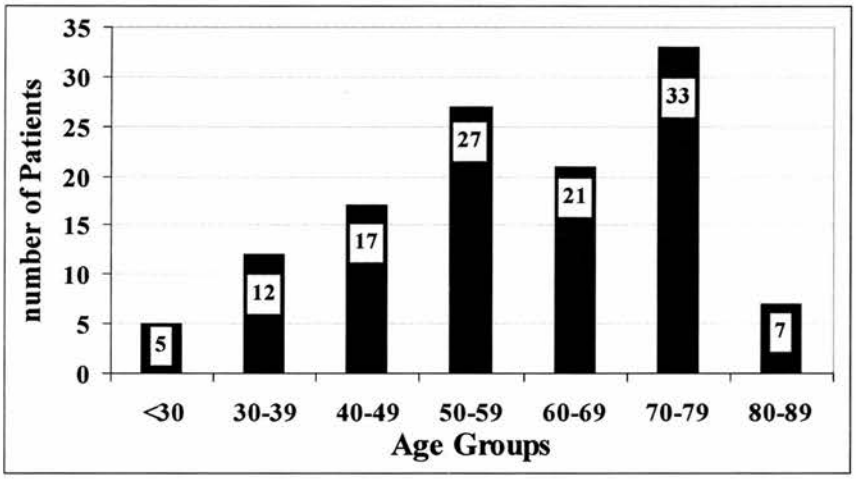

Figure 4.2; Age distribution in 10 years period

4.7.1.1. Comparison between age groups according to survival

The patients were grouped according to age: young patients (less than 65 years) and old patients (65 years or more) according to UKRR reports. A log rank test showed that survival of the two groups differed significantly (p=0.001) **(Figure 4.3).** The mortality rate was more than 2 times higher in old patients compared with young patients (42.5% vs. 17.6% **Table 4.6**.

Age groups	Number of patients	Number dead in 2 years	% dead in 2 years	Log rank p-value
<65 years	68	12	17.6	0.001
≥65 years	54	23	42.5	

Table 4.6; Mortality in young and old age groups

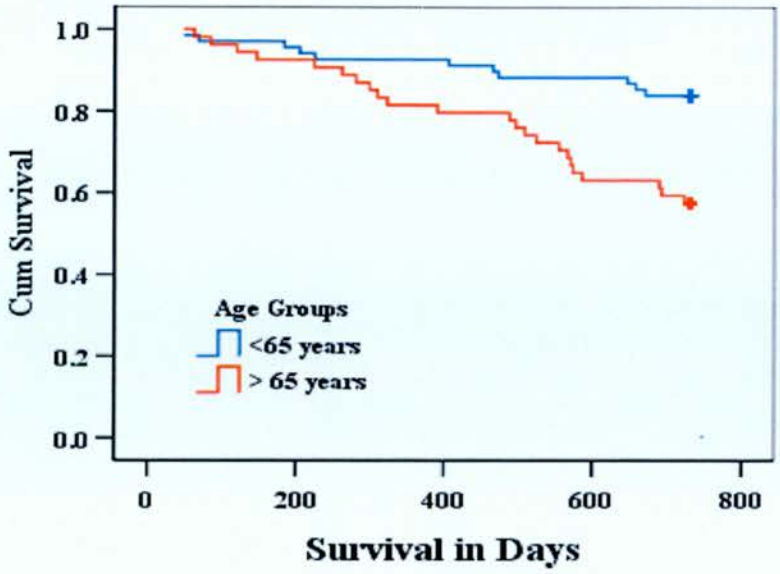

Figure 4.3; Survival difference between age groups (p=0.001)

4.7.2. Primary renal diagnosis

The distribution of patients according to primary renal diagnosis with median age is shown in **Table 4.7** and **Figure 4.4.** The most frequent group is glomerulonephritis 26.2% with median age 63 years. Multisystem disease has the oldest median age at 71 years. Only 7 patients included in this study were known to be diagnosed as diabetic nephropathy. List of primary renal diagnosis with ERA-EDTA code, number of patients and percentage in each diagnosis are shown in **Table 4.8.**

PRD groups	N0	%	Median age (IQR)
Glomerulonephritis	32	26.2	63 (46-74)
Interstitial Nephritis	29	23.8	53 (43-64)
Multisystem disease	25	20.5	71 (57-75)
Diabetic Nephropathy	7	5.7	66 (57-75)
Unknown and Others	29	23.8	58 (42-73)

Table 4.7; Distribution of primary renal diagnosis into 5 main groups

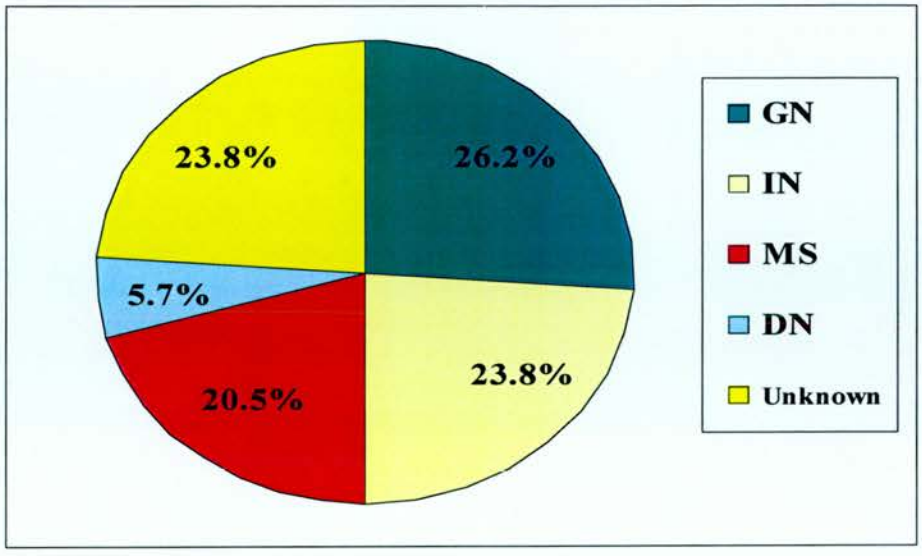

Figure 4.4; Percentage of primary renal disease

ERA-EDTA Primary Renal Diagnosis	Code	No	%
Aetiology unknown	0	25	20.5
Polycystic kidneys, adult (dominant)	41	12	9.9
Renal vascular disease due to hypertension	72	8	6.7
Ischaemic renal disease/cholesterol embolism	75	8	6.7
IgA nephropathy	12	7	5.7
glomerulonephritis; histologically examined, not given above	19	7	5.7
Diabetic glomerulosclerosis or diabetic nephropathy	81	7	5.7
Membranous nephropathy	14	5	4.1
glomerulonephritis; histologically not examined	10	4	3.3
FSGS with nephrotic syndrome	17	4	3.3
Pyelonephritis due to vesico-ureteric reflux without obstruction	24	4	3.3
Renovascular disease	70	4	3.3
Pyelonephritis due to congenital obstructive uropathy +/- vesico-ureteric reflux	22	3	2.5
Renal hypoplasia (congenital)	60	3	2.5
Interstitial nephritis	30	2	1.6
Hereditary nephritis with nerve deafness (Alport's syndrome)	51	2	1.6
Renal vascular disease due to malignant hypertension	71	2	1.6
Goodpastures syndrome	86	2	1.6
Pyelonephritis - cause not specified	20	1	0.8
Pyelonephritis associated with neurogenic bladder	21	1	0.8
Pyelonephritis due to acquired obstructive uropathy	23	1	0.8
Pyelonephritis due to urolithiasis	25	1	0.8
Interstitial nephropathy due to analgesic drugs	31	1	0.8
Medullary disease including nephronophthisis	43	1	0.8
Renal vascular disease due to polyarthritis	73	1	0.8
Wegener's granulomatosis	74	1	0.8
Myelomatosis/light chain deposit disease	82	1	0.8
Lupus erythematosus	84	1	0.8
Tubular necrosis (irreversible) or cortical necrosis	90	1	0.8
Traumatic or surgical loss of kidney	96	1	0.8
Interstitial nephritis	99	1	0.8

Table 4.8; List of primary renal diagnosis of 122 patients

4.7.2.1. Comparison between the primary renal diagnosis groups according to outcome

The log rank test for primary renal diagnosis was significant (p=0.0001) **(Figure 4.5)**. The highest mortality rate was among those with a diagnosis of multisystem disease 60% were dead at the end of the study with median survival 1.8 year. The interstitial nephritis group had the lowest mortality rate 6.8% (median survival not recorded during study) **(Table 4.9)**.

PRD groups	Number of patients	Number dead in 2 years	% dead in 2 years	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
PRD							0.0001
GN	32	8	25				
IN	29	2	6.8				
MS	25	15	60	1.8	1.1	2.4	
DN	7	2	28.5				
Unknow n	29	8	27.5	>2			

Table 4.9; Mortality differences between primary renal diagnosis groups

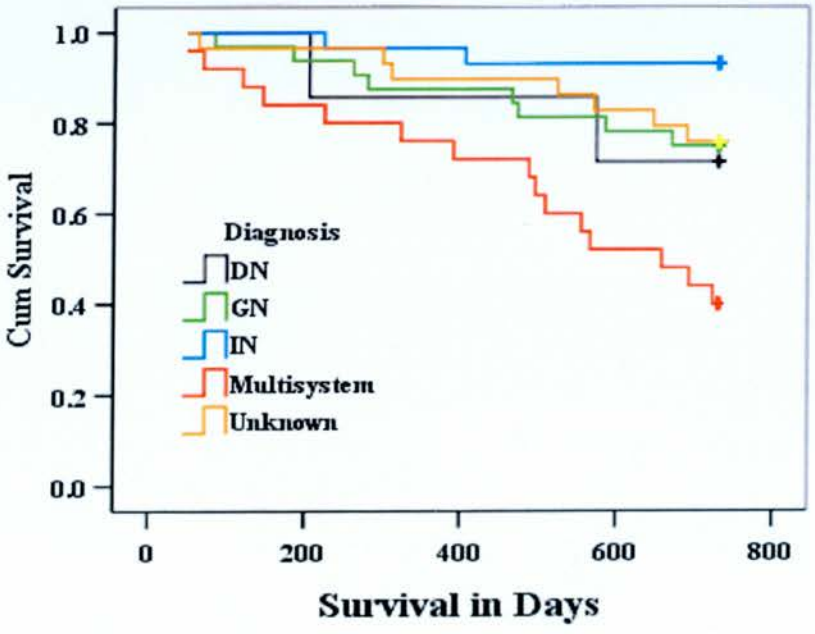

Figure 4.5; Survival curve for primary renal diagnosis (p=0.0001)

4.7.3. Subjective global assessment

According to total SGA score patients were classified into 3 groups **(Figure 4.6)**. Group A or severely malnourished patients (score 1 to 2) included only 4 patients (3.3%) with median age 62 years. Group B or moderately malnourished patients (score 3 to 5) included 41 patients with median age of 59 years. Group C or well nourished patients (score 6 to 7) was the most frequent group, 77 patients (63.1%), with the higher median age 71 years **(Table 4.10)**.

variables	N0	%	Median age (IQR)
Severe malnutrition	4	3.3	62 (46-77)
Moderate malnutrition	41	33.6	59 (43-75)
Normal	77	63.1	71 (57-75)

Table 4.10; SGA groups and median age

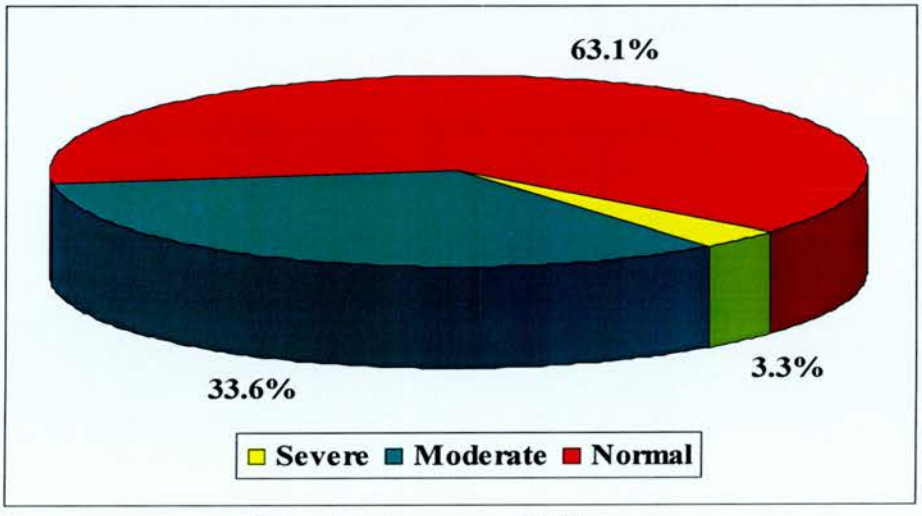

Figure 4.6; Percentage of SGA groups

4.7.3.1. SGA Correlations

The relationship between SGA total score and other continuous data was investigated using Pearson product-moment correlation coefficient (**Table 4.11**). A strong positive correlation was found between SGA and nutritional indices (serum albumin, BMI, MAMC and TSF), a higher score of SGA was associated with a higher level of serum urea, serum albumin, and higher measurements of BMI, MAMC, and TSF **(Figures 4.7,8,9,10,11)**. There was no significant correlation between SGA and

either age or serum cholesterol. There was strong negative correlation between SGA and CRP, the higher score of SGA was associated with lower levels of CRP **(Figure 4.12)**

Variables	SGA	
	r-value	**p-value**
Age	-0.050	0.586
Cholesterol	-0.001	0.992
Urea	0.312	0.0001
Albumin	0.405	0.0001
CRP	-0.252	0.005
BMI	0.412	0.0001
MAMC	0.307	0.001
TSF	0.355	0.0001

Table 4.11; Correlation between SGA total score and continuous variables
(r-value= Pearson Correlation)

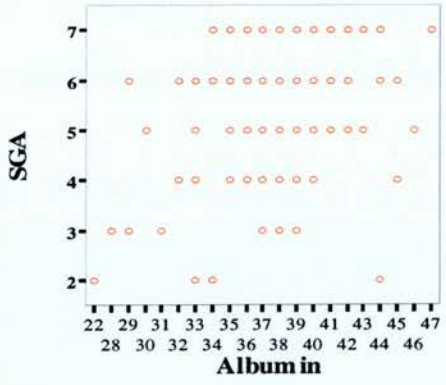

Figure 4.7; Scatter-plot of SGA vs. Albumin

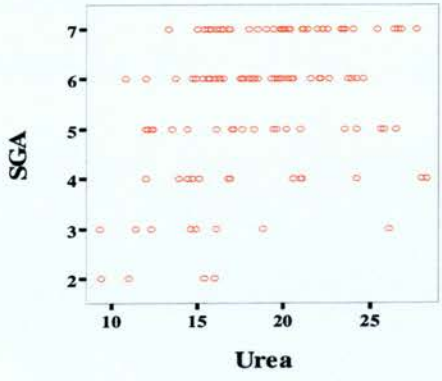

Figure 4.8; Scatter-plot of SGA vs. Urea

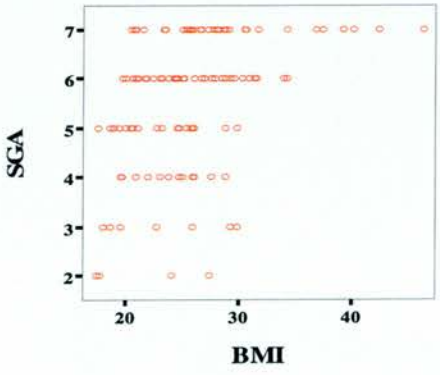

Figure 4.9; Scatter-plot of SGA vs. BMI

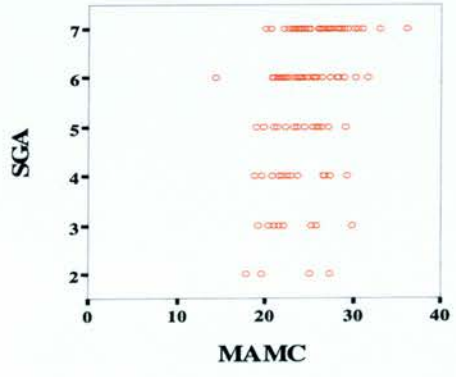

Figure 4.10; Scatter-plot of SGA vs. MAMC

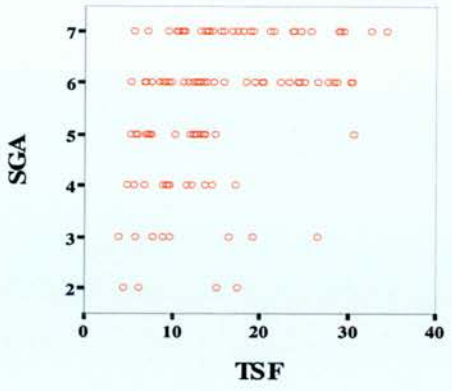

Figure 4.11; Scatter-plot of SGA vs. TSF

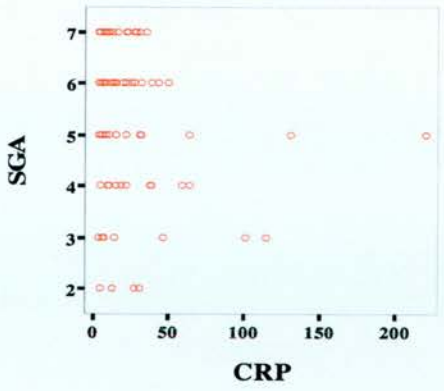

Figure 4.12; Scatter-plot of SGA vs. CRP

4.7.3.2. Univariate analysis and characteristic of malnourished and well nourished patients

4.7.3.2.1. Univariate analysis of malnourished patients

Due to the small number of severely malnourished patients, I have combined both severely and moderately malnourished patients into one "malnourished group" which included 45 patients according to SGA classification. The analysis showed that mortality at two years was 44.4% and the main cause of death was cardiovascular disease (55%) followed by infection (35%) **(Table 4.12)**. The analysis also showed that age, comorbidity, serum cholesterol, primary renal diagnosis, and time spent on dialysis prior to the start of the study were all significantly associated with death in malnourished patients. The mortality of malnourished patients was associated with the presence of ischaemic heart disease, peripheral vascular disease and cerebrovascular disease **(Table 4.13)**.

4.7.3.2.2. Univariate analysis of well nourished patients

Univariate analysis of well nourished patients showed that the mortality at two years was 19.4%. Cardiovascular disease was the leading cause of death (60%) followed by infection (20%) **(Table 4.12)**. The analysis revealed that age, comorbidity, modality, serum albumin serum urea, MAMC, were all associated with death among well nourished patients. Moreover presence of congestive cardiac failure, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and diabetes all significantly influenced the survival of the well nourished group of patients **(Table 4.14)**.

Cause of death	Malnourished		Well nourished	
	no	%	no	%
Cardiovascular disease	11	55	9	60
Infection	7	35	3	20
Malignancy	0	0	2	13.3
Others	2	10	1	6.7

Table 4.12; Causes of death in well nourished and malnourished patients

	Cohort n=45	survivors n=25	Dead by n=20	p value & statistic test
Median age (years) (IQR)	59 (44-75)	46 (39-60)	75 (62-79.5)	p=0.0001 M-W
Age≥65 years	17 (37.8)	4 (16)	13 (65)	p=0.001 χ^2
Gender				p=0.428 χ^2
Male	31 (68.9)	16 (64)	15 (75)	
Female	14 (31.1)	9 (36)	5 (25)	
Mode of RRT				p=0.815 χ^2
Haemodialysis	41 (91.1)	23 (92)	18 (90)	
Peritoneal dialysis	4 (8.9)	2 (8)	2 (10)	
Mean Albumin (g/l)	36.5 SD 4.6	37.4 SD 4.2	35.3 SD 5	p=0.13 T-test
Mean Cholesterol (mmol/l)	4.2 SD 1.1	4.5 SD 1.1	3.8 SD 0.9	p=0.034 T-test
Median CRP (mg/l) (IQR)	13 (5-31)	7 (5-35)	19.5 (10-30)	p= 0.11 M-W
Mean Urea (mmol/l)	17.5 SD 5.1	17.8 SD 5.3	17.2 SD 5	p=0.589 T-test
BMI (kg/m2)	23 (19.5-25.8)	21.9 (19.1-26.7)	24.3 (19.9-25.7)	p= 0.936 M-W
Mean MAMC (cm)	23.3 SD 3.2	23 SD 3.2	23.6 SD 3.2	p=0.579 T-test
Time on dialysis (years)	3.3 (2.2-7.6)	4 (2.5-9.8)	2.3 (1.6-4.9)	p= 0.010 M-W
PRD				p=0.020 χ^2
Glomerulonephritis	11 (24.4)	6 (24)	5 (25)	
Interstitial Nephritis	9 (20)	9 (36)	0	
Multisystem diseases	13 (28.9)	4 (16)	9 (45)	
Diabetic nephropathy	1 (2.2)	0	1 (5)	
Unknown	11 (24.4)	6 (24)	5 (25)	
Comorbid Conditions				
Ischaemic heart disease	18 (40)	6 (33.3)	12 (60)	p=0.014 χ^2
Congestive cardiac failure	8 (17.8)	2 (8)	6 (30)	p=0.055 χ^2
Peripheral vascular disease	9 (20)	2 (8)	7 (35)	p=0.024 χ^2
Cerebrovascular disease	11 (24.4)	3 (12)	8 (40)	p=0.030 χ^2
Diabetes	5 (11.1)	1 (4)	4 (20)	p=0.090 χ^2
Khan Score				p=0.0001 χ^2
Low	15 (33.3)	15 (60)	0	
Medium	9 (20)	4 (16)	5 (25)	
High	21 (46.7)	6 (24)	15 (75)	

Table 4.12; Characteristics and univariate analysis of malnourished patients χ^2=Chi square test, M.W= Mann Whitney test

	Cohort n=77	survivors n=62	Dead by n=15	p value & statistic test
Median age (years) (IQR)	63 (46-71)	58 (44-70)	70 (57-75)	p=0.024 M-W
Age≥65 years	37 (48.1)	27 (43.5)	10 (66.7)	p=0.108 χ^2
Gender				p=0.740 χ^2
Male	44 (57.1)	36 (58.1)	8 (53.3)	
Female	33 (42.9)	26 (41.9)	7 (46.7)	
Mode of RRT				p=0.006 χ^2
Haemodialysis	68 (86.2)	54 (87.1)	14 (93.3)	
Peritoneal dialysis	9 (11.7)	8 (12.9)	1 (6.7)	
Mean Albumin (g/l)	38.6 SD 3.1	39.1 SD 3.1	36.8 SD 2.5	p=0.005 T-test
Mean Cholesterol (mmol/l)	4.2 SD 0.9	4.2 SD 0.9	4.1 SD 0.9	p=0.568 T-test
Median CRP (mg/l) (IQR)	6 (5-18)	5 (5-12)	16 (7-32)	p= 0.004 M-W
Mean Urea (mmol/l)	19.4 SD 3.6	19.8 SD 3.7	17.4 SD 2.3	p=0.021 T-test
BMI (kg/m2)	26.1 (23.7-29.2)	26.6 (24.1-29)	24.2 (23.1-29.6)	p= 0.410 M-W
Mean MAMC (cm)	25.2 SD 3.3	25.6 SD 3.2	23.5 SD 3.3	p=0.039 T-test
Time on dialysis (years)	4.7 (3.2-9.2)	4.8 (3.2-9.2)	3.5 (3-11.2)	p= 0.563 M-W
PRD				p=0.068 χ^2
Glomerulonephritis	21 (27.3)	18 (29)	3 (20)	
Interstitial Nephritis	20 (26)	18 (29)	2 (13.3)	
Multisystem diseases	12 (15.6)	6 (9.7)	6 (40)	
Diabetic nephropathy	6 (7.8)	5 (8.1)	1 (6.7)	
Unknown	18 (23.4)	15 (24.2)	3 (20)	
Comorbid Conditions				
Ischaemic heart disease	24 (31.2)	13 (21)	11 (73.3)	p=0.0001 χ^2
Congestive cardiac failure	10 (13)	4 (6.5)	6 (40)	p=0.001 χ^2
Peripheral vascular disease	13 (16.9)	5 (8.1)	8 (53.3)	p=0.0001 χ^2
Cerebrovascular disease	13 (16.9)	5 (8.1)	8 (53.3)	p=0.001 χ^2
Diabetes	16 (20.8)	10 (16.1)	6 (40)	p=0.041 χ^2
Khan Score				p=0.001 χ^2
Low	28 (36.3)	26 (41.9)	2 (13.3)	
Medium	20 (26)	19 (30.6)	1 (6.7)	
High	29 (37.7)	17 (27.4)	12 (80)	

Table 4.14; Characteristics and univariate analysis of well nourished patients χ^2=Chi square test, M.W= Mann Whitney test

4.7.3.3. Comparison between SGA groups according to survival

Figure 4.13 shows the significant influence of SGA groups on survival (p=0.001). Patients classified as well nourished (total SGA score = 6 to 7) had the lowest mortality rates with 19.4% and median survival >2 years. On the other hand the severely malnourished group had the highest mortality rate 75% with median survival of 1.3 years. The mortality rate of moderate malnourished group was 41.4% with median survival >2 years **(Table 4.15).**

When the same analysis was carried out but this time comparing well nourished patients with malnourished patients (severe and moderate malnourished groups) the mortality rate among the malnourished group was 2 times greater than well nourished group (44.4% vs. 19.4%) **(Figure 4.14)**.

SGA	Number of patients	Number dead in 2 years	% dead in 2 years	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
							0.001
Severe	4	3	75	1.3	0.4	2.2	
Moderate	41	17	41.4	>2			
Normal	77	15	19.4	>2			
							0.001
malnourished	45	20	44.4				
Normal	77	15	19.4				

Table 4.15; Mortality differences according to SGA groups

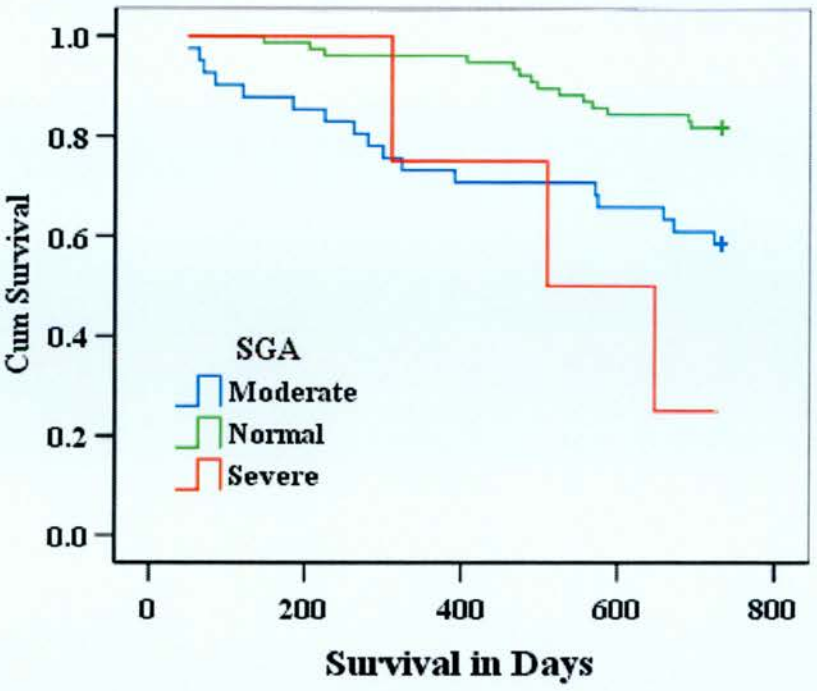

Figure 4.13; Survival curve for 3 groups of SGA (p=0.001)

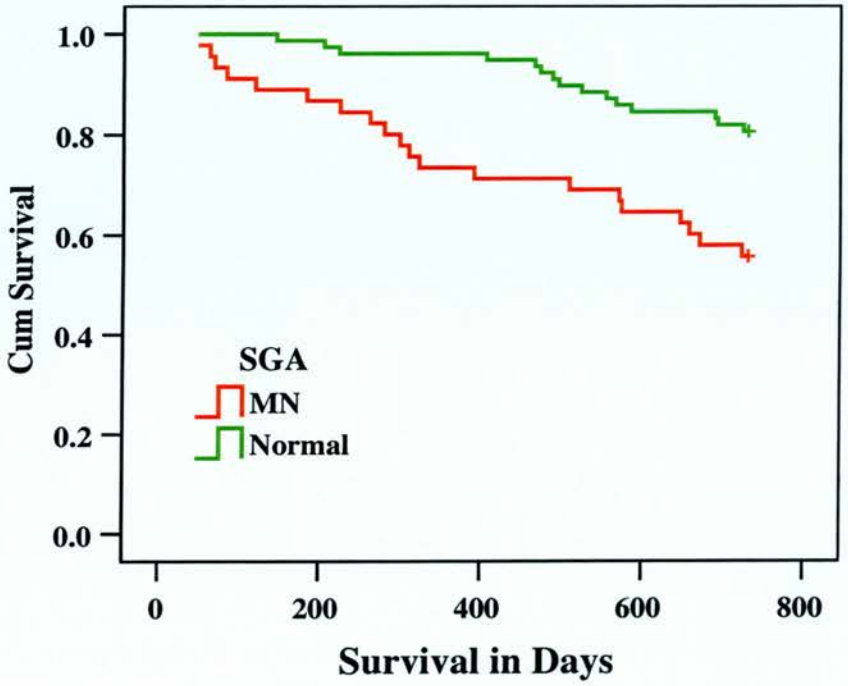

Figure 4.14; Survival curve for 2 groups of SGA (p=0.001)

4.7.4. Comorbidity

4.7.4.1. Frequency of comorbid disease

Ischaemic heart disease (angina and myocardial infarction) was the most frequent comorbidity, found in 42 patients (34.4%). Cerebrovascular disease, which was found in 24 patients (19.6%), was the second most common comorbidity. 21 (17.2%) patients had diabetes, but only 7 patients (5.7%) were diagnosed with diabetic nephropathy **(Figure 4.15)**

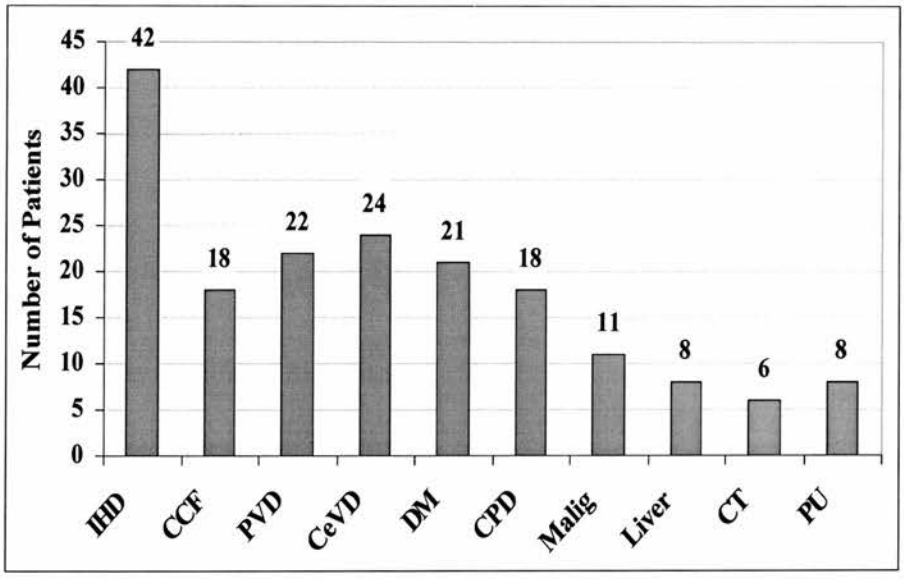

Figure 4.15; Distributions of comorbid illnesses

The frequency of comorbidity in males was higher than females except for diabetes mellitus, which was slightly higher in females (11vs.10). The frequency of cerebrovascular disease was equal in both sexes (12 vs.12), CT disease was equally common in both sexes but the number of patients involved was very small (3 vs.3) **(Figure 4.16).**

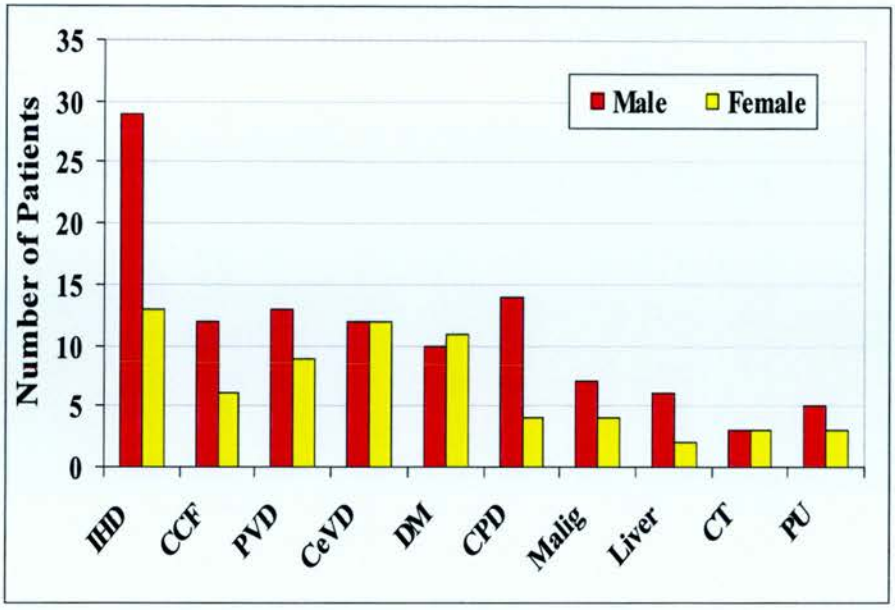

Figure 4.16; Distribution of comorbid illnesses in both sexes

The frequency of comorbid conditions was higher in the older age group (≥ 65 years) than in younger patients except for peptic ulcer disease for which the frequency was equal, although the number of patients involved was very small (4 vs. 4). In the case of liver disease the frequency was higher in the younger age group but the number of patients was small (6 vs. 2 for liver disease) **(Figure 3.17)**.

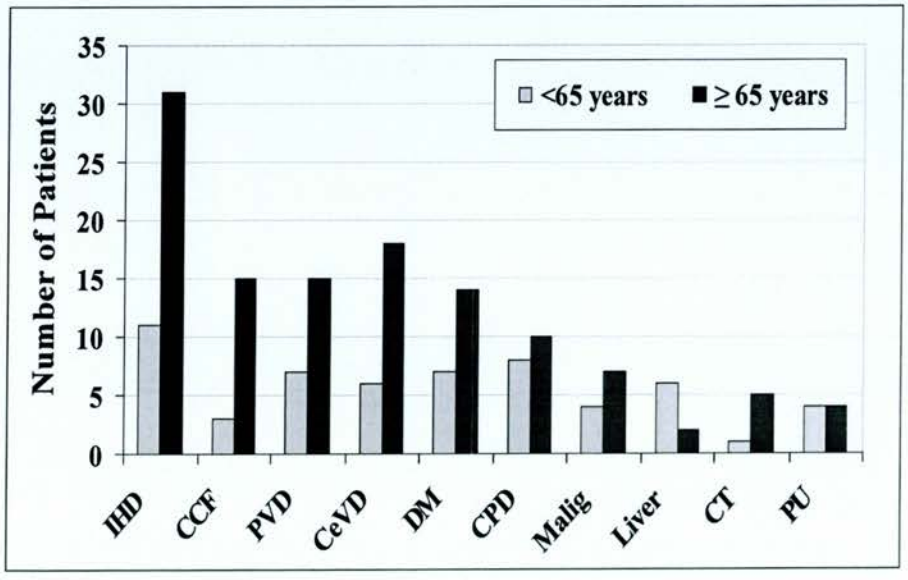

Figure 4.17; Frequency of comorbidity and age group difference

4.7.4.2. Outcome according to comorbid conditions

The influence of comorbid illnesses on survival is illustrated in **(Table 4.16)**. Ischaemic heart disease showed a significant difference (p=0.0001) in survival between the 2 groups of patients, those with ischaemic heart disease had mortality rate of 57.7% with median survival 1.8 year (p=0.0001) **(Figure 4.18)**. Patients with congestive cardiac failure had a mortality rate of 66.6% with median survival 1.5 year **(Figure 4.19).**

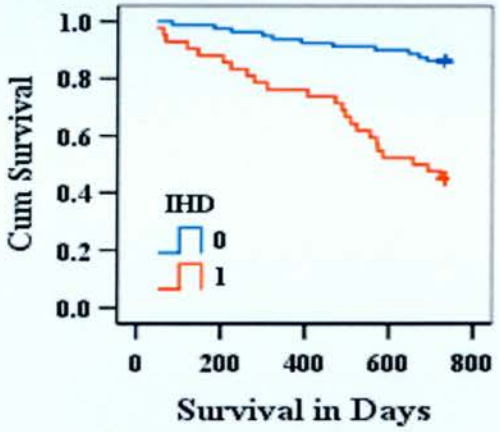

Figure 4.18 Survival curve for Ischaemic heart disease (IHD) (p=0.0001)

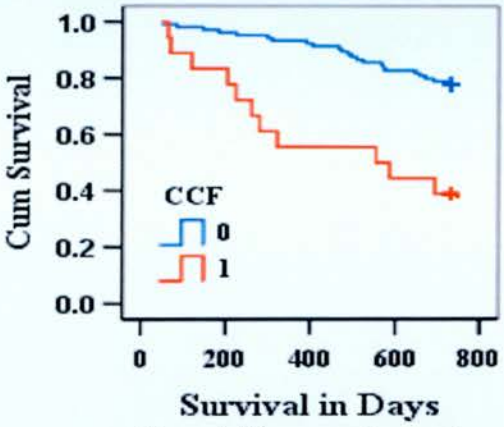

Figure 4.19; survival curve for Congestive cardiac failure (CCF) (p=0.0001)

Figure 4.20 shows a significant difference (p=0.029) in survival between diabetic and non diabetic patients (mortality rates 47.6% compared with 24.7%). Also a significant survival difference in patients with peripheral vascular disease, and cerebrovascular disease from those who were without these comorbid conditions **(Figure 4. 21, 22)**.

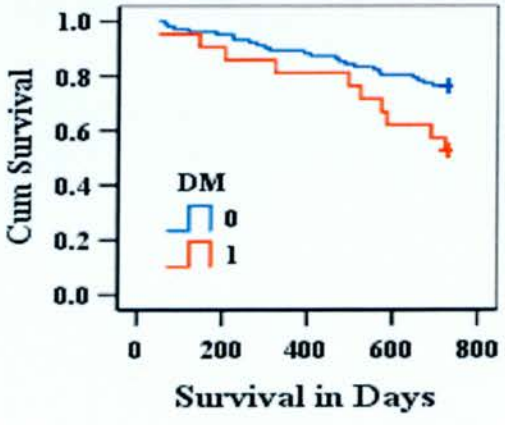

Figure 4.20; Survival curve for Diabetes mellitus (DM) (p=0.029)

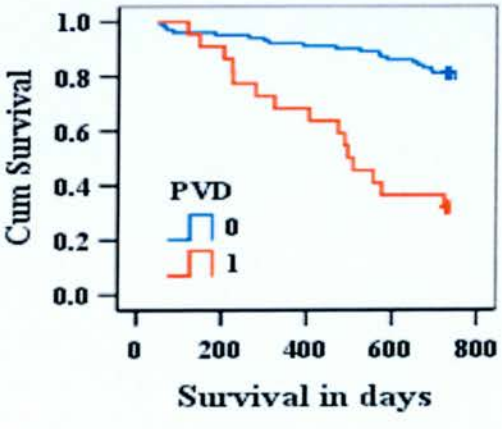

Figure 4.21; Survival curve for Peripheral vascular disease (PVD) (p=0.0001)

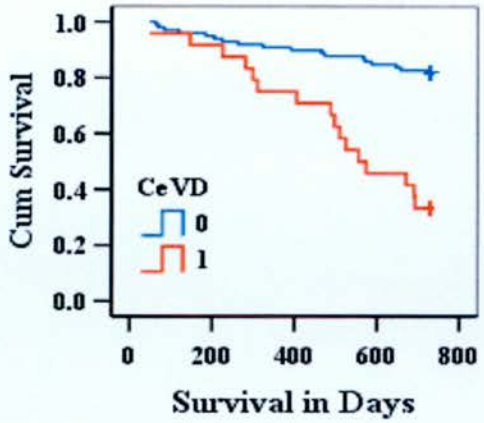

Figure 4.22; Survival curve for cerebrovascular disease (CeVD) (p=0.0001)

Malignancy, chronic pulmonary disease and connective tissue diseases did not show a significant influence on survival **(Figures 4. 23, 24, 25)**.

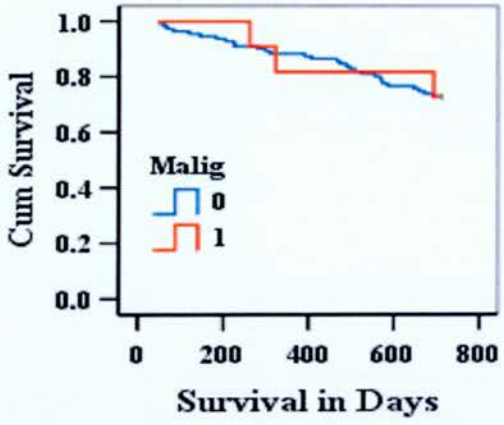

Figure 4.23; Survival curve for Malignancy (p=0.934)

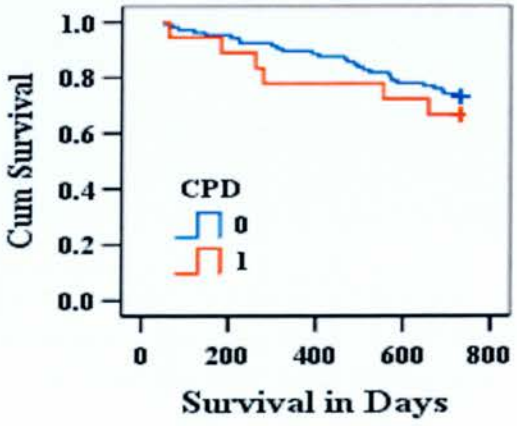

Figure 4.24; Survival curve for Chronic pulmonary disease (CPD) (p=0.508)

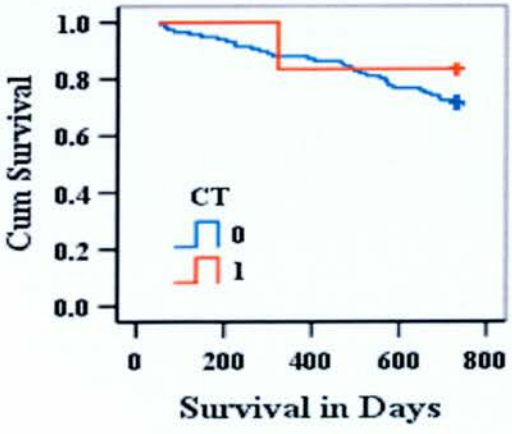

Figure 4.25; Survival curve for Connective tissue disease (p=0.558)

Comorbid conditions	Number of patients	Number dead in 2 years	% dead in 2 years	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
IHD							0.0001
Yes	42	23	57.7	1.8			
No	80	12	15	>2			
CCF							0.0001
Yes	18	12	66.6	1.5	0.1	>2	
No	104	23	22.1				
PVD							0.0001
Yes	22	15	68.1	1.3	1.1	1.6	
No	100	20	20	>2			
CeVD							0.0001
Yes	24	16	66.6	1.5	0.9	>2	
No	98	19	19.3	>2			
DM							0.029
Yes	21	10	47.6				
No	101	25	24.7	>2			
Malignancy							0.934
Yes	11	4	36.6	>2			
No	111	31	27.9				
CPD							0.508
Yes	18	7	38.8	>2			
No	104	28	23				
CT Disease							0.558
Yes	6	1	16.6				
No	116	34	29.3	>2			

Table 4.16; Mortality difference in different comorbid conditions

4.7.5. Khan score

According to Khan score 50 patients (41%) were classified as high risk and they were the oldest with median age 72 years. The proportion of low risk and medium risk patients was 35.2% and 23.8% with median age 45 and 64 respectively (**Table 4.17**).

Khan score	No	%	Median age	IQR
Low Risk	43	35.2	45	38-57
Medium Risk	29	23.8	64	51-70
High Risk	50	41	72	62-76

Table 4.17; Khan Score groups and median age

4.7.5.1. Comparison between the groups of comorbidity score according to survival

There was a significant influence of comorbidity on survival (p=0.0001) between the groups of Khan score **(Figure 4.26)**. The two years mortality was 5.1% in the low risk group, but increased by 4 and 12 fold in the medium and high risk groups respectively **(Table 4.18)**.

Comorbidity scores	Number of patients	Number dead in 2 years	% dead in 2 years	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
Khan							0.0001
Low	43	2	4.6				
Medium	29	6	20.6				
High	50	27	54.0	1.8	1.7	2	

Table 4.18; Mortality difference between Khan Score risk groups

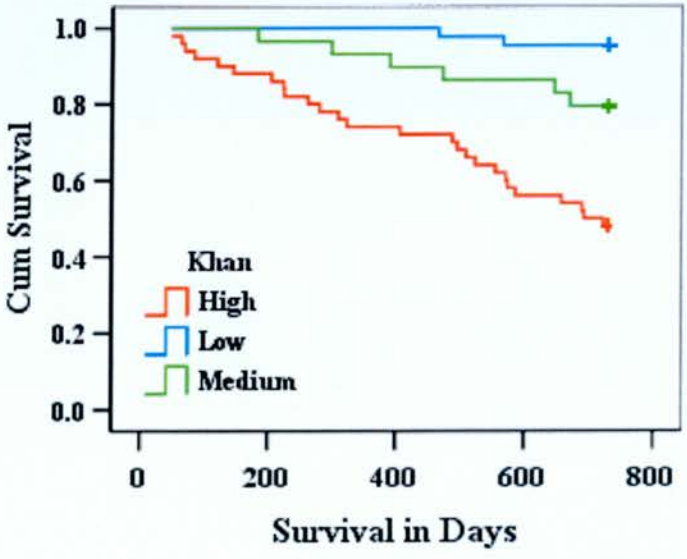

Figure 4.26; survival curve for Khan Score (p=0.0001)

4.8. Multivariate analysis of patient mortality

The Cox regression model of survival analysis was used to identify those independent factors associated with death. Survival analysis was performed for 122 dialysis patients. The independent variables used in the multivariate analysis were gender, mode of RRT, serum-, albumin, urea, cholesterol, and CRP, primary renal diagnosis, time spent on dialysis before starting the study, BMI, MAMC, SGA (1=severe malnutrition, 2= moderate malnutrition, and 3= normal), and comorbidity evaluated by Khan Score for classification into 3 risk groups (mild, medium and high) as this included age, so age was not included in the analysis. The main outcome was 2 years patient survival.

Each 1mg/l increase in serum CRP increased the chance of death by 1%. The risk of death was significantly (p=0.011) increased by 2.4 times in moderately malnourished (SGA score =3 to 5) compared with reference or normal group (SGA score = 6 to 7), and was 5.1 times higher in the severely malnourished group (SGA = 1 to 2). Comorbidity according to Khan score showed that the risk of death was significantly (p=0.0001) increased by 4.9 times and over 17 times in the medium and high risk groups respectively compared with the low risk group (**Table 4.19**).

In order to see the effect of every single comorbid diseases upon survival a separate multivariate analysis was carried out, including the same variables that had been described in the above analysis but entering all the comorbid diseases instead of Khan score and adding age as independent factor. The analysis revealed the same results from the above analysis, and in addition, patients who had cerebrovascular and peripheral vascular diseases had increased risk of death 2.1 and 2.2 times greater than patients who were without these diseases. Moreover, each additional year in patient's age increased their chance of death by 5% (**Table 4.20**).

Other variables analysed which did not contribute significantly to multivariate model were gender, mode of RRT, serum-albumin, serum urea, serum cholesterol, BMI, MAMC, primary renal disease, and time on dialysis before the study had started.

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
CRP (mg/l)	0.007	1.01	1.0	1.02
SGA	.011	Ref		
Moderate malnourished		2.41	1.14	5.07
Severe malnourished		5.16	1.44	18.42
Khan	0.0001	Ref		
Medium risk group		4.92	0.97	24.85
High risk group		17.88	4.18	76.37

Table 4.19: Cox regression survival analysis Khan Score model

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Age (years)	0.003	1.05	1.01	1.09
CRP (mg/l)	0.049	1.01	1.0	1.02
SGA	.036	Ref		
Moderate malnourished		2.5	1.16	5.38
Severe malnourished		3.15	0.84	11.81
Cerebrovascular disease	0.048	2.14	1.01	4.56
Peripheral vascular disease	0.043	2.27	1.02	5.03

Table 4.20; Cox regression survival analysis all comorbid conditions model

4.9. Comparison of Survival and mean age of Edinburgh prevalent patients and study patients of the same year

As the study in this chapter was cross sectional in design and therefore subject to the possibility of selection bias during the initial recruitment, it is possible that only those dialysis patients who were generally healthier agreed to participate. A comparison of the mean age and one year survival showed that there was no difference in the one year survival of 122 patients included in this study and overall survival of all 298 prevalent dialysis patients in Edinburgh in the same year (87.7% vs. 87.4%). However, the median age in this study was higher than overall prevalent dialysis patients (**Table 4.21**).

	Study patients	Overall Edinburgh prevalent patients
Number of patients	122	298
Median age	58.5	54.9
1 year survival %	87.7	87.4

Table 4.21; Age and 1 year survival of study patients and all prevalent patients in Edinburgh

4.10. Hospitalisation

Hospitalisation rates may reflect the quality of dialysis care because patient morbidity affects the frequency and the duration of hospital stay. Moreover hospital stay is a common occurrence in dialysis patients.

The percentage of live time at risk spent in hospital (time from starting of the study 11/4/2005 to either death or end of study 11/4/2007) was calculated for each patient as had been explained in chapter 2. The Kruskal Wallis test used to compare the median percentages between the groups (p-value<0.05 was significant). The overall median percentage of time spent in hospital was 2.4% (0.3% – 7.2%) (Mean = 5.8%). Only 15 patients (12.3%) were not admitted to the hospital in a period of two years.

4.10.1. Correlation of hospitalisation and continuous variables

Pearson correlation showed that time spent in hospital in 2 years was associated positively with CRP (the high levels of CRP associated with more time spent in

hospital). Inversely serum albumin and total SGA score were negatively associated with hospital stay. High serum albumin level associated with less time spent in hospital also the better nutritional status measured according to SGA score associated with less hospital admissions (**Table 4.22**).

	CRP	Serum albumin	SGA
Days spent in hospital			
Pearson Correlation	0.359	- 0.383	-0.295
p-value	0.0001	0.0001	0.001

Table 4.22; Pearson correlations of hospitalisation

4.10.2. Comparison between groups according to hospitalisation percentage

The median percentage of time at risk spent in hospital was highest for old patients (1.9% under 65 years, 4% ≥65 years). Hospitalisation was affected by the nutritional status according to SGA classification. Patients classified as severely malnourished had the highest median percentage of time at risk spent in hospital 10.1% (however this group included only 4 patients) compared with 3.6% and 1.9% for moderately malnourished and well nourished groups respectively. The analysis showed a significant difference in median percentage of time spent in hospital between risk groups, where the lowest percentage was for patients with low risk (1.6%), followed by moderate risk (2.5%) and the highest for the high risk group at 4% (**Table 4.23**).

	Cases no	Cases %	Median % time spent in hospital	IQR	Kruskal-Wallis Test (p-value)
Age group					0.039
<65 years	68	55.7	1.9	0.2 - 4.2	
≥65 years	54	44.3	4	0.5 – 11.9	
SGA					0.005
Normal	77	63.1	1.9	0.2 – 4.4	
Moderate MN	41	33.6	3.6	0.5 – 10.8	
Severe MN	4	3.3	10.1	6.4 – 19.2	
Khan					0.045
Low	43	35.2	1.6	0.1 – 3.1	
Medium	29	23.8	2.5	0.2 – 5.2	
High	50	41	4	0.6 – 12.3	

Table 4.23; Hospitalisation according to age groups, SGA groups and Khan Score groups

There was no significant difference in the median percentage of time at risk spent in hospital between gender, modality and primary renal diagnosis groups (**Table 4.24**).

	Cases no	Cases %	Median % time spent in hospital	IQR	Kruskal-Wallis Test (p-value)
Gender					0.505
Male	75	61.5	2.6	0.5 – 7.1	
Female	47	38.5	1.6	0.1 – 7.6	
Modality					0.768
Peritoneal dialysis	13	10.7	0.6	0 – 13	
Haemodialysis	109	89.3	2.4	0.5 – 5.5	
Primary renal diagnosis					0.409
Glomerulonephritis	32	26.2	2.5	0.4 – 7.4	
Interstitial Nephritis	29	23.8	1.6	0.2 – 4.6	
Multisystem disease	25	20.5	3.8	0.7 – 10	
Diabetic Nephropathy	7	5.7	0.6	0 – 5.3	
Unknown	29	23.8	2.4	0.4 – 8	

Table 4.24; Hospitalisation percentage according to gender, modality and primary renal diagnosis

4.11. Summary

Although this is a cross sectional study, the survival results are typical of those seen in bigger survival studies. The one year survival rate was the same for the study patients and all prevalent dialysis patients in the same hospital at the same year (87.7% vs. 87.4%). The mortality of 122 prevalent patients was 28.7% at two years. The main cause of death was cardiovascular disease (57.1%), followed by infection (28.6%), others (8.6%), and malignancy (5.7%).

Univariate analysis revealed that age, comorbidity, primary renal diagnosis, SGA, time on dialysis prior study started, serum-albumin, urea, cholesterol and CRP were all associated with mortality. Of all comorbid conditions the analysis showed that ischaemic heart disease, congestive cardiac failure, peripheral vascular disease cerebrovascular disease, and diabetes had an influence on patient survival.

Multivariate analyses revealed that age, comorbidity, SGA, and CRP were significantly associated with death. Cerebrovascular and peripheral vascular diseases were contributory factors to patient survival.

The overall median percentage of hospitalisation was 2.4%. Hospitalisation was markedly increased in older, malnourished patients, and in patients with high comorbidity.

All in all this study found that measuring SGA provides significant additional information. Beyond that the main factors that influence patient survival were comorbidity, nutritional status, and CRP.

Chapter 5

Results and Outcome of Incident RRT Patients in 2003 and 2004

5.1. Abstract

Introduction

The morbidity and mortality of the high risk group is a general concern. The presence of diseases such as cardiac disease, cerebrovascular disease, diabetes, and malignancy has been recognized to play a big role in increasing the mortality risk in dialysis patients.

Aim

To examine factors associated with survival in a detailed analysis of the cohort commencing dialysis in south east Scotland in 2003 and 2004.

Method

183 patients started RRT in South East Scotland in 2003-2004, 156 haemodialysis, 25 peritoneal dialysis and 2 as pre-emptive transplants. Comorbidity was scored by Charlson, Khan and Davies methods. Univariate and multivariate Cox regression was used to identify the independent predictors of survival. The main outcomes were overall survival and hospitalisation.

Results

The median age was 65 years. The gross mortality was 26.2% at one year 38.2% at two years and 47.5% at the end of the study. (period of 2 – 4 years). Cardiovascular disease accounted for 40% of all deaths. Multivariate analysis revealed that age, comorbidity, permanent access, and initial serum cholesterol were independent predictors of mortality. Hospitalisation percentage was higher in more elderly patients.

Conclusion

Age, severity of comorbidity, initial access and initial serum cholesterol were important predictors of survival of patients starting RRT in 2003 and 2004 in the Renal Unit of the Royal Infirmary of Edinburgh.

5.2. Introduction

Survival is the ultimate outcome measure of the success of RRT and may be used as a tool to compare performance among different health care providers. The influence of age, comorbidity, serum albumin and primary renal diagnosis are important to be considered for measuring the survival in RRT patients. Early death is a useful data to be collected to compare the survival between different centers. In particular comparison of European data with those from the United States Renal Data System (USRDS) excludes those dying in the first 90 days.

5.3. Methods

Patients: - This cohort study included 183 patients who started RRT in 2003 and 2004 at the RIE renal unit (85 patients started RRT in 2003 and 98 patients in 2004).

Demographic data: - age, sex, mode of first RRT, definitive access, referral to nephrologist, primary renal diagnosis.

Laboratory measurements: - the following parameters were measured on all patients prior to starting dialysis treatment: serum concentrations of urea, albumin, creatinine, haemoglobin, cholesterol and CRP. These measurements were performed in the routine clinical laboratory of our unit.

Instruments of data collection, coding and grouping: - (I) the primary renal diagnosis code was chosen from the list issued by European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). Diagnosis in ERA-EDTA list has previously been placed into 5 categories [(1) Glomerulonephritis (2) Interstitial nephritis (3) Multisystem diseases (4) Diabetic nephropathy (5) Unknown causes]. (II) The death causes code was chosen from the list issued by ERA-EDTA that has been placed in main 5 groups: [(1) Cardiovascular/vascular causes (2) Infection (3) Malignancy (4) Unknown causes (5) Other known causes].

Data on comorbid conditions: - were represented into 3 different comorbid scores. The Charlson index does not include age, which was entered into the analysis as a

separate variable, and angina was included within the Charlson scoring system. Davies score is similar to Charlson using age as separate variable in the analysis but has fewer comorbid conditions than the Charlson index. Another analysis used Khan score, which includes age to stratify the patients into low-, medium-, and high risk groups; therefore, age was not used in the analysis when Khan score was used as an independent variable. In-addition, all comorbid conditions collected were included in separate multivariate analysis to evaluate the effect of each of them on survival.

Follow-up period: - patients in this study were followed until 1/1/2007, a period of minimum 2 years for those who started in December 2004 and maximum 4 years for those who started in January 2003 or until death. The median time of treatment (median time of follow up) was 817 days *(27.2 months)* IQR 334 to 1102 days *(11.5 to 36.7 months)*, minimum 7 days and maximum 1440 days *(0 to 48 months)*.

Hospitalisation: - was studied by assessing the frequency of hospitalisation and its total duration in days for exactly 2 years. Hospitalisation was defined as any hospital admission that included at least one overnight stay in the hospital. The admission day was counted as one full hospitalisation day but the discharge day was not. Therefore, the minimum duration of hospitalisation per admission was 1 day. Percentage of hospitalisation was the sum of all hospital admissions to the sum of total duration of treatment.

5.4. Patient mortality

183 patients were studied of whom 48 (26.2%) were dead by the end of one year, 70 (38.2%) at 2 years and 87 (47.5%) by the end of the study (period of 2 – 4 years). In order to make these figures more directly comparable with the USRDS, death patients within the first 90 days of RRT were excluded and the mortality at the end of one year was 35 (20.6%), 57 (33.5%) at 2 years and at by the end of the study was 74 (43.5%) **(Table 5.1),** survival curve of those incident patients started dialysis in 2003 and 2004 shown in **Figure 5.1.** All statistics presented later in this chapter refers to overall mortality including those dying within 90 days of starting RRT unless otherwise stated.

Duration of RRT	Overall Mortality n=183		Excluding 90days deaths n=170	
	n	%	n	%
90 days	13	7.1%	-	-
6 month	25	13.7%	12	7.1%
1 year	48	26.2%	35	20.6%
18 months	61	33.3%	48	28.2%
2 years	70	38.2%	57	33.5%
End of study	87	47.5%	74	43.5%

Table 5.1; Mortality of patients receiving RRT in 2003 and 2004

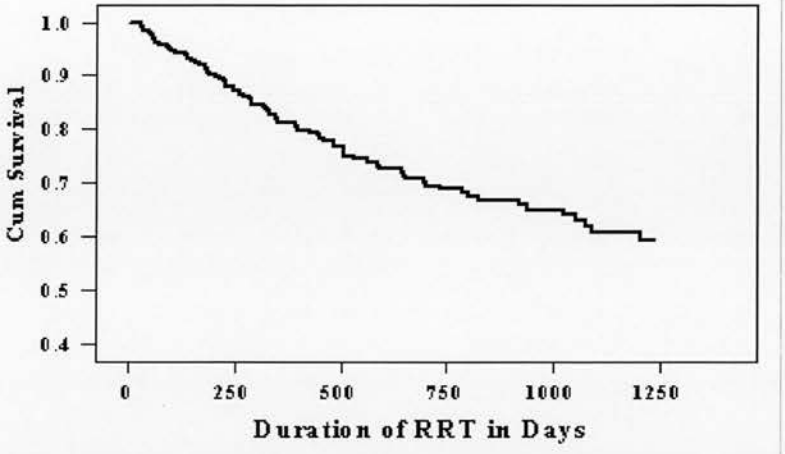

Figure 5.1; Survival curve of incident patients started RRT in RIE in 2003 and 2004 from 1/1/2003 until 1/1/2007.

5.5. Causes of death

Infection was the leading cause of death in the first year 38.3%, followed by cardiovascular 34%, other causes 21.3%, unknown cause 4.3% and malignancy 2.1%. However, the highest proportion of death at the end of the study was cardiovascular disease 40.7%, followed by infection 29.1%, other causes 16.2%, unknown cause 9.3%, and malignancy 4.7 % (**Table 3.2**). Table 3.3 list causes of death with ERA-EDTA codes, and the number of patients and percentage in each cause.

Cause of death	One year		End of the study	
	n	%	n	%
Cardiovascular	16	34	35	40.7
Infection	17	38.3	25	29.1
Malignancy	1	2.1	4	4.7
Unknown	2	4.3	8	9.3
Others	10	21.3	15	16.2

Table 5.2; Cause of death at one year and at end of the study

ERA-EDTA Cause of Death	Code	no	(%)
Cardiovascular/vascular causes			
Cardiac arrest Unknown cause	15	21	(24.4%)
Other causes of cardiac failure	14	4	(4.7%)
Myocardial ischemia and infarction	11	6	(7%)
Cardiovascular rupture aneurysm	26	1	(1.1%)
Cerebrovascular accident	22	3	(3.5%)
Infection			
Pulmonary infection	31	10	(11.7%)
Septicaemia	35	13	(15.2%)
Infection else where	34	1	(1.1%)
Peritonitis	39	1	(1.1%)
Malignancy	67	4	(4.7%)
Cause of death uncertain/ not determined	0	8	(9.3%)
Others			
Gastro-intestinal Haemorrhage	23	2	(2.4%)
Liver failure-unknown cause	46	1	(1.1%)
Bowel ischemia	99	1	(1.1%)
Perforation of colon	72	1	(1.1%)
Dementia	69	1	(1.1%)
Hyperkalemia	12	1	(1.1%)
ESRF treatment withdrawn for medical reasons	54	7	(8.4%)

Table 5.3; List of causes of death of 183 patients

5.6. Demographic data

Main clinical and demographic characteristics with summary statistics for all 183 incident patients are shown **in Table 5.4 and 5.5** below. Descriptive data are presented as mean ± SD, median (min and max) and number (%).

Variable	Number	Percentage
Age groups		
<65 years	86	47
≥ 65 years	97	53
Gender		
Male	100	55
Female	83	45
Access (haemodialysis+ peritoneal dialysis)		
Permanent access	89	49.2
Temporary access	92	50.8
Access haemodialysis		
Permanent access	64	41
Temporary access	92	59
Modality		
Haemodialysis	156	85.2
Peritoneal dialysis	25	13.7
Pre-emptive Transplant	2	1.1
Nephrology Referral with in		
3 months		
Referred	132	72.9
Not-Referred	49	27.1
6 months		
Referred	125	69.1
Not-Referred	56	30.9

Table 5.4; Basic clinical and demographic characteristic of study

Variable	Median(min-max)	Mean ± SD
Age (years)	65 (18-88)	
CRP (mg/l)	15 (2-368)	
Creatinine (µmol/l)	616 (174-1479)	
Albumin (g/l)		33.6 ± 5.5
Urea (mmol/l)		25.3 ± 8.6
GFR (ml/min)		7.8 ± 2.3
Haemoglobin (g/l)		9.2 ± 1.4
Cholesterol mmol/l		4.4 ± 1.2

Table 5.5; Summary statistic of the study population at initiation of RRT

5.7. Comparisons between the groups, according to survival

5.7.1. Continuous parameters

The normally distributed parameters at start of RRT were compared by the independent t tests and for non-parametric (not normally distributed) variables the Mann-Whitney test was used and their results presented in **Tables 5.6 and 5.7** below. The significant differences between the two groups when they started their RRT were in age, serum albumin, serum cholesterol, serum creatinine and CRP.

variable	Alive	Deceased	p-value
Albumin (g/l)	35.5 ± 5.1	31.5 ± 5.3	0.0001
Urea (mmol/l)	25.9 ± 8.2	24.6 ± 8.9	0.31
eGFR (ml/min)	7.7 ± 2.3	8 ± 2.4	0.42
Cholesterol (mmol/l)	4.7 ± 1.2	4.1 ± 1.5	0.0001
Haemoglobin (g/l)	9.2 ± 1.5	9.1 ± 1.3	0.63

Table 5.6; Parametric comparison of baseline serum parameters (mean ± SD), by survival

Variable	Alive	Deceased	p-value
Age (years)	55 (40-68)	72 (64-78)	0.0001
CRP (mg/l)	8 (4-19)	31 (8-82)	0.0001
Creatinine (μmol/l)	669 (512-811)	574 (418-692)	0.001

Table 5.7; Non-parametric comparison of baseline serum parameters (median &IQR), by survival

3.7.2. Age

The median age in this study was 65 years (IQR 50-75). The age of the patients was distributed in 10 years periods. The highest percentage of incident patient starting RRT was at age group 70 to 79 (28.9%) where as the lowest percentage of incident patients starting RRT was at age group 20 to 29 (7.1%) **(Figure 5.2)**

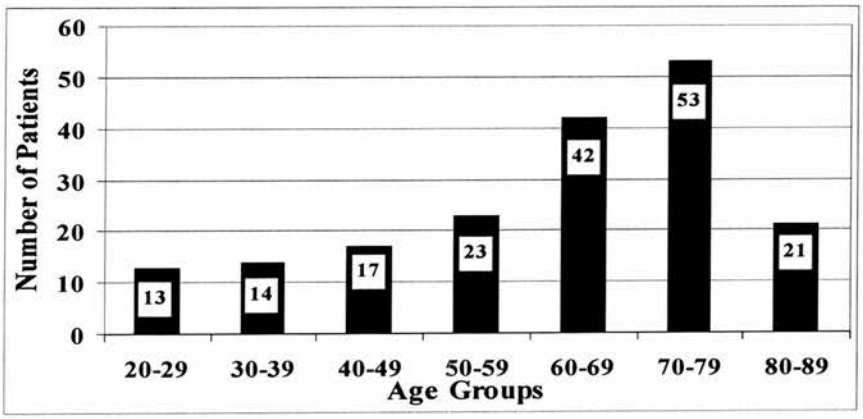

Figure 5.2; Age distribution in 10 years period

5.7.2.1. Comparison between age groups according to survival

According to the UKRR reports the patients were classified into 2 age groups young patients (less than 65 years) and old patients (65 years or more). The two age groups differed significantly (p=0.0001) **(Figure 5.3)**. Mortality at end of study in old patients (≥ 65 years) was 64.9% with median survival of 2 years (0.9 to 3) in contrast the mortality rate in young patients (<65 years) was 27.9% (median survival not recorded during study) **Table 5.8**.

Age groups	Number starting RRT	Number dead by 1/1/2007	% dead by 1/1/2007	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
<65 years	86	24	27.9				0.0001
≥65 years	97	63	64.9	2	0.9	3	

Table 5.8; Number and percentage of young and old age groups

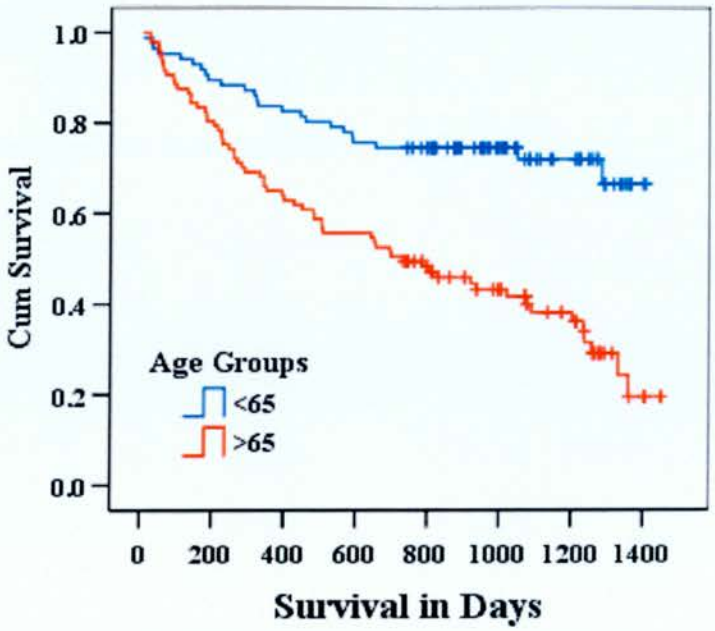

Figure 5.3; Survival differences between young and old age groups (p=0.0001)

5.7.3. Primary renal diagnosis

Based on ERA-EDTA diagnosis code and in order to facilitate analysis of the data the aetiology of ESRD was categorized into 5 main subgroups **(chapter 2).** The distribution of all 183 patients according to these subgroups with median age of each group is shown in **(Table 5.9)** and **(Figure 5.4)**. The most frequent group is

multisystem diseases 28.4% with median age of 67 years that includes those who presented with renal vascular disease, hypertensive nephropathy, kidney tumour, and multiple myeloma. Unknown diagnosis, in which the exact cause of ESRD could not be identified, included the most elderly patients with median age 74 years. **Table 5.10** shows the list of primary renal diagnosis with ERA-EDTA code, number and percentage of patients.

Primary Renal Diagnosis	No	%	Median age (IQR)
Glomerulonephritis	41	22.4%	62 (41-71)
Interstitial Nephritis	34	18.6%	59 (42-70)
Multisystem Disease	52	28.4%	67 (56-79)
Diabetic Nephropathy	19	10.4%	61 (45-68)
Not known and Others	37	20.2%	74 (65-80)

Table 5.9; Distribution of primary renal diagnosis into 5 main groups

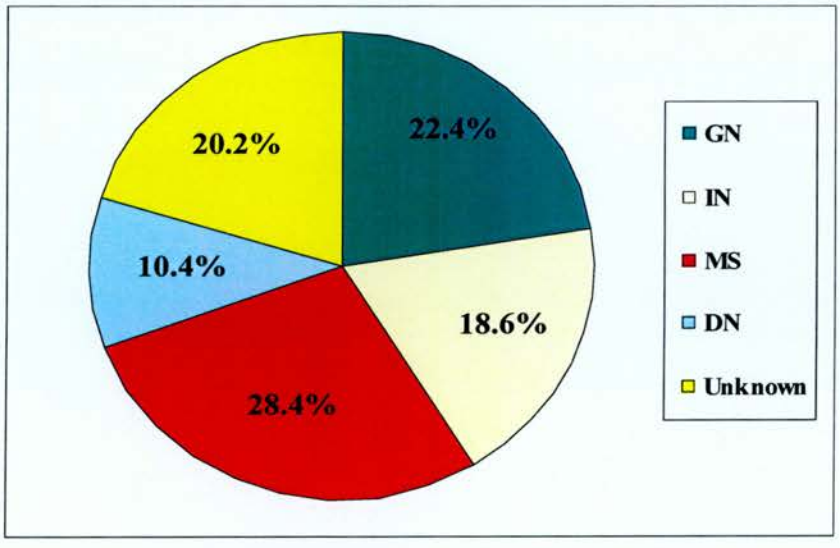

Figure 5.4; Percentage of primary renal diagnosis

The distribution of gender according to primary renal diagnosis is shown in **Figure 5.5**. **Figure 5.6** shows the distributions of primary renal diagnosis according to age in 10 years period. Unknown cause and other multisystem disease diagnosis are more frequent among older age groups; and interstitial nephritis is more prevalent in younger patients and in women.

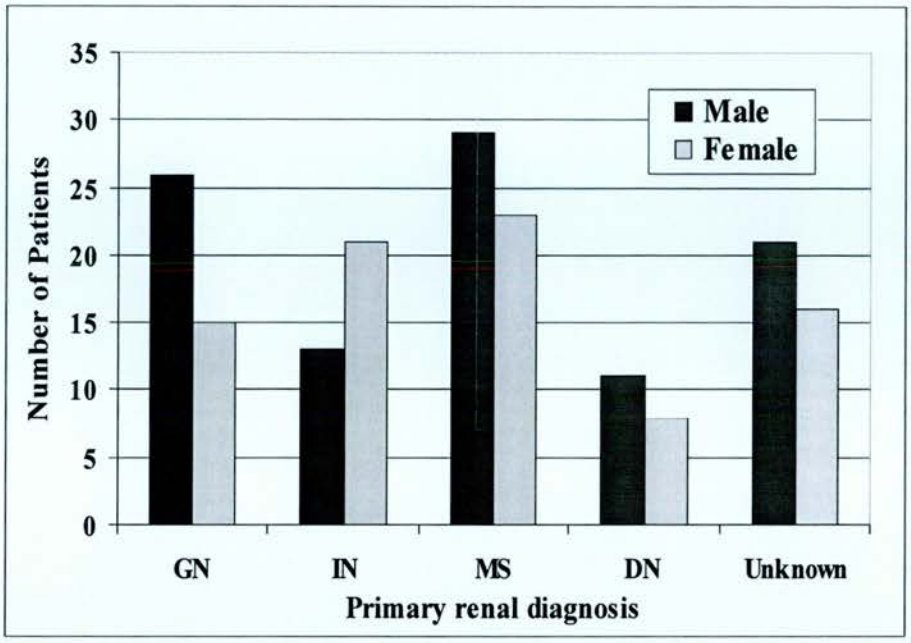

Figure 5.5; Gender differences of primary renal diagnosis

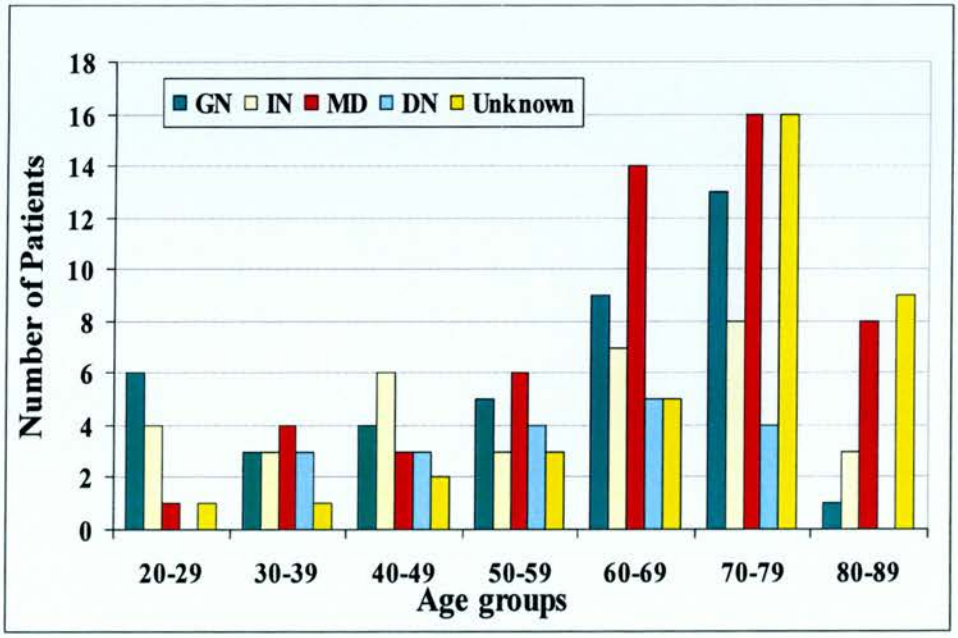

Figure 5.6; Age group differences of primary renal diagnosis

ERA-EDTA Primary Renal Diagnosis	Code	No	%
Chronic renal failure; aetiology uncertain/unknown/unavailable	0	36	19.7
Diabetic glomerulosclerosis or diabetic nephropathy	80	19	10.4
Ischaemic Renal Disease/ cholesterol embolism	75	15	8.2
Renal vascular disease due to hypertension	72	15	8.2
Polycystic kidneys; adult type (dominant)	41	11	6.1
IgA Nephropathy	12	9	4.9
Pyelonephritis due to vesico-ureteric reflux without obstruction	24	7	3.9
Membranous Nephropathy	14	6	3.3
Renal vascular disease-type unspecified	70	5	2.8
Myelomatosis/light chain deposit disease	82	5	2.8
Focal Segmental glomerulosclerosis with nephrotic syndrome	17	5	2.7
Goodpasture's Syndrome	86	5	2.7
Drug induced interstitial nephropathy	39	4	2.2
Renal vascular disease-due to other causes	79	4	2.2
Renal vascular disease due to malignant hypertension	71	4	2.2
Crescentic Glomerulonephritis	16	3	1.7
Pyelonephritis cause not specified	20	3	1.7
Lupus erythematosus	84	3	1.5
Glomerulonephritis histologically not examined	10	2	1.1
Glomerulonephritis, histologically examined	19	2	1.1
Pyelonephritis due to acquired obstructive uropathy	23	2	1.1
Interstitial nephritis (not Pyelonephritis) unspecified	30	2	1.1
Traumatic or surgical loss of kidney	96	2	1.1
Renal vascular disease due to polyarthritis	73	2	1.1
Wegener's Granulomatosis	74	2	1.1
Membranoproliferative glomerulonephritis type 1	15	1	0.5
Pyelonephritis due to urolithiasis	25	1	0.5
Interstitial nephritis due to cyclosporine A	33	1	0.5
Cystic kidney disease - type unspecified	40	1	0.5
Hereditary nephritis with nerve deafness (Alport's syndrome)	51	1	0.5
Nephrocalcinosis and hypercalcaemic nephropathy	93	1	0.5
Kidney tumours	95	1	0.5
Henoch-Schonlein purpura	85	1	0.5
Haemolytic uraemic syndrome (including Moschvowitz Syndrome)	88	1	0.5
Other identified renal disorders	99	1	0.5

Table 5.10; List of primary renal diagnosis of 183 patients

5.7.3.1. Comparison between the primary renal diagnosis groups according to outcome

In the univariate analysis survival was significantly (p=0.037) influenced by primary renal disease (**Figure 5.7**). Patients with interstitial nephritis had the lowest mortality rate 29.4% followed by diabetic nephropathy 36.8%. Patients with unknown diagnosis had the highest mortality rate 62.2% with median survival of 2.1 years followed by multisystem disease group 57.7% with median survival 3.2 years (**Table 5.11**).

PRD groups	Number starting RRT	Number dead by 1/1/2007	% dead by 1/1/2007	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	0.037
GN	41	17	41.5	3.6	2.9	4.3	
IN	3.4	10	29.4				
MS	52	30	57.7	3.2	1.7	4.8	
DN	19	7	36.8				
Unknown	37	23	62.2	2.1	0.9	3.4	

Table 5.11; Mortality difference between primary renal diagnosis groups

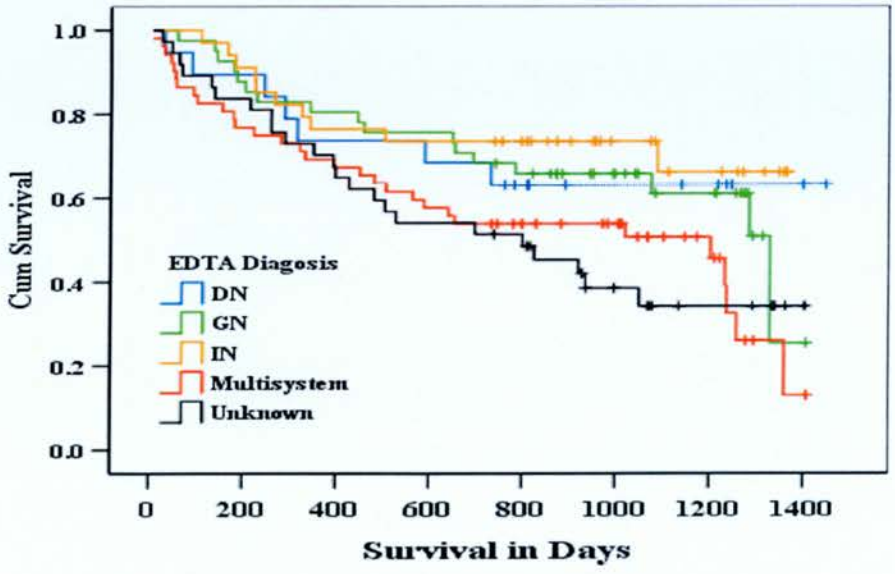

Figure 5.7; Survival curve for primary renal diagnosis groups (p=0.037)

5.7.4. Comorbidity

5.7.4.1. Frequency of comorbid diseases

The most frequent comorbid disease was congestive cardiac failure which occurred in 70 (38.2%) patients; cardiovascular disease [myocardial infarction and angina] was found in 62 patients. The number of patients with diabetes was 44 (24%), but only 19 (10.4%) patients were diagnosed with diabetic nephropathy **(Figure 5.8)**. The list of all collected comorbid conditions was shown in chapter 2.

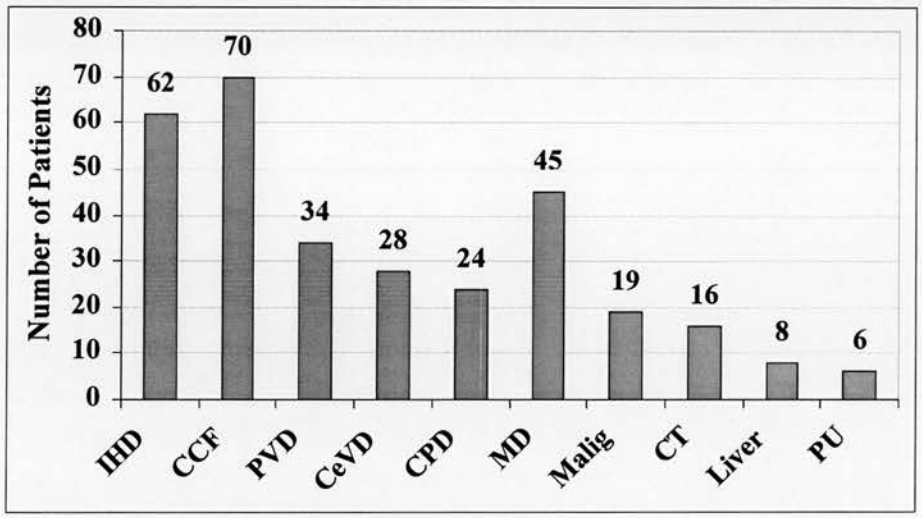

Figure 5.8; Distribution of comorbid illnesses

The frequency of comorbid conditions was high in older age group (≥ 65 years) except for peptic ulcer disease the frequency was equal although the number of patients involved was very small (3 vs. 3). In case of liver disease the frequency was higher in younger age group but the number of patients was small (5 vs. 3 for liver disease) **(Figure 5.9)**. The frequency of comorbidity according to primary renal diagnosis is shown in **Figure 5.10**. Patients diagnosed with other multisystem disease are at highest risk of serious comorbid conditions including cardiovascular comorbidity in forms of ischaemic heart disease (angina and myocardial infarction), congestive cardiac failure, peripheral vascular disease, and cerebrovascular disease, and malignancy.

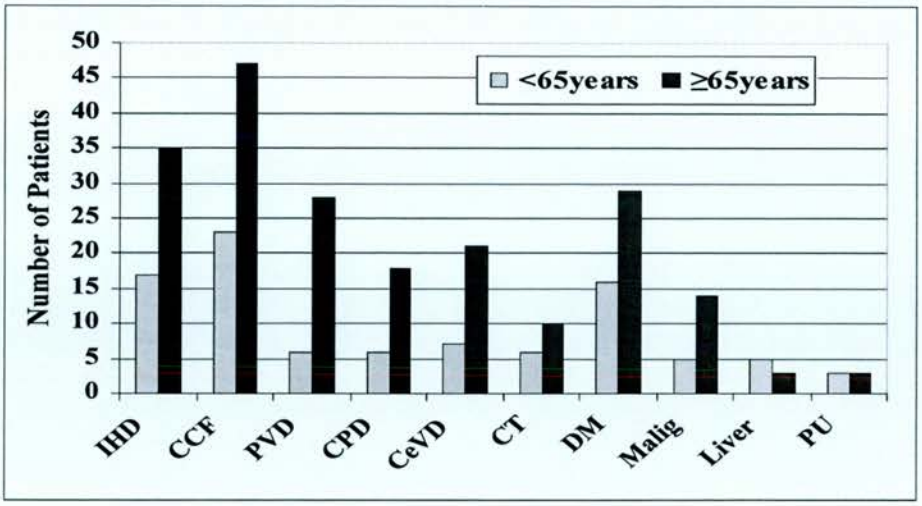

Figure 5.9; Frequency of comorbidity and age group difference

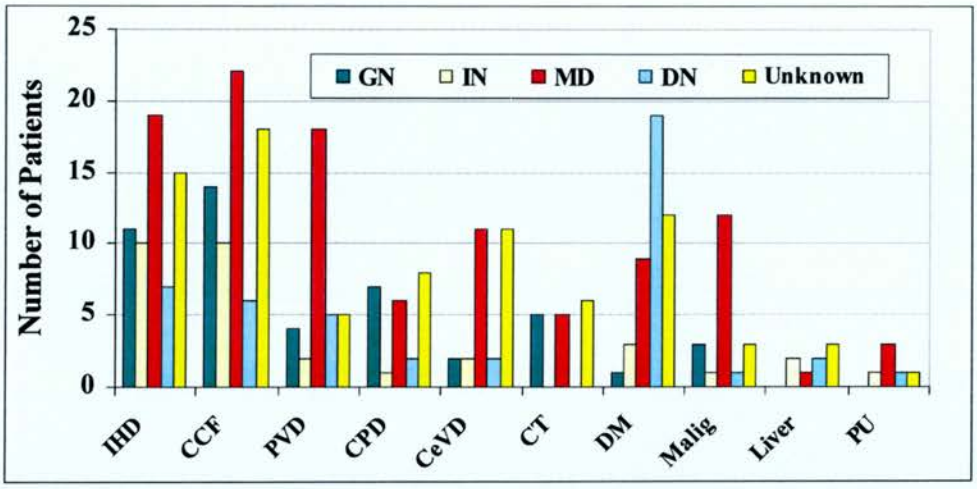

Figure 5.10; Frequency of Comorbidity according to primary renal diagnosis

Distribution of comorbid condition according to 10 years age group is shown in **(Figures 5.11)**. All the comorbid conditions show the same pattern of distribution in 10 years period as the graphs show the minimal comorbidity among the youngest age group and the maximum number was among the patients between 70-79 years then start to decline in the age group 80-89 years this decline could be due to lower number of patients or may be those patient are die before they are considered as candidate for dialysis treatment or that elderly patients with significant comorbidity are not considered for RRT. The exception of distribution pattern of comorbid conditions in relation to age groups was shown in malignancy as the maximum number of patients was in age group 60-69.

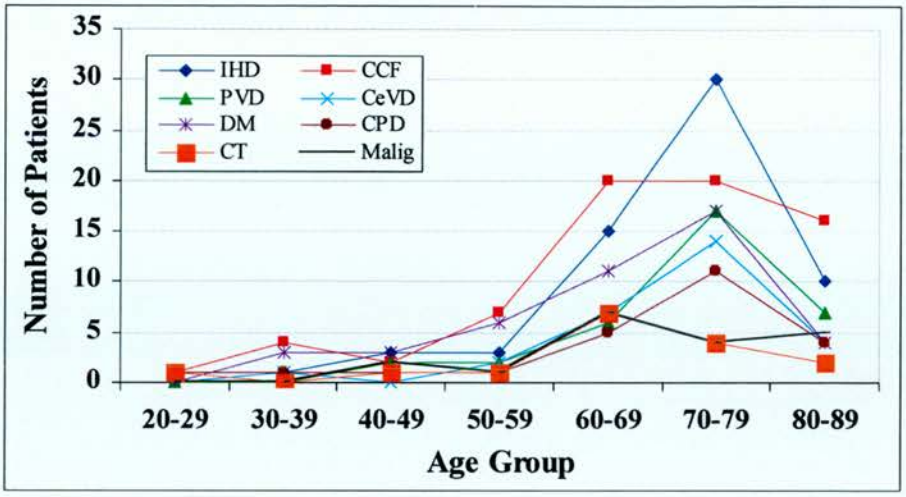

Figure 5.11; Distribution of comorbid condition in relation to 10 years age group

5.7.4.2. Outcome according to comorbid conditions

There was a significant difference in survival between those patients with and with out congestive cardiac failure; 75.7% of those with congestive cardiac failure had died (median survival 1 year), while for those with out congestive cardiac failure the mortality was 30.1%. **(Figure 5.12)**. Patients with ischaemic heart disease had a median survival of 1.3 (0.4 to 2.2) year **(Figure 5.13)**.

Patients with malignancy had mortality rate of 68.4% and median survival of 1.2 year (0.8 to 1.6) **(Figure 5.19)**. Also, significant survival difference were demonstrated between patients who started RRT with or without peripheral vascular disease **(Figure 5.14)**, cerebrovascular disease **(Figure 5.15)**, chronic pulmonary disease **(Figure 5.16)**, and connective tissue disease **(Figure 5.17) (Table 5.12)**. There was no significant difference (p=0.390) in survival between patients who started RRT with diabetes (median 2.5 years) and those who started RRT without diabetes (median 3.4 years) **(Figure 5.18)**

Comorbid conditions	Number starting RRT	Number dead by 1/1/2007	% dead by 1/1/2007	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
CCF							0.0001
Yes	70	53	75.7	1	0.5	3.1	
No	113	34	30.1				
IHD							0.0001
Yes	62	43	69.4	1.3	0.4	2.2	
No	121	44	36.4				
PVD							0.008
Yes	34	24	70.6	2	0.4	3.5	
No	149	63	42.3	3.7	2.8	4.6	
CeVD							0.020
Yes	28	20	71.4	1.5	0.1	3.2	
No	155	67	43.2	3.6	2.9	4.3	
CPD							0.002
Yes	24	18	75	1	0.2	1.8	
No	159	69	43.4	3.5	3.1	3.8	
CT Disease							0.003
Yes	16	12	75	1.2	0.6	1.7	
No	167	75	44.9	3.4	2.9	3.9	
Malignancy							0.009
Yes	19	13	68.4	1.2	0.8	1.6	
No	164	74	45.1	3.4	2.9	3.9	
DM							
Yes	44	33	52.3	2.5	1.5	3.5	0.390
No	139	64	46	3.4	3	3.8	

Table 5.12; Mortality difference in different comorbid conditions, CCF=congestive cardiac failure, IHD=ischemic heart disease, CeVD=cerebrovascular disease, CPD=chronic pulmonary disease, CT diseases=connective tissue disease, DM, diabetes mellitus.

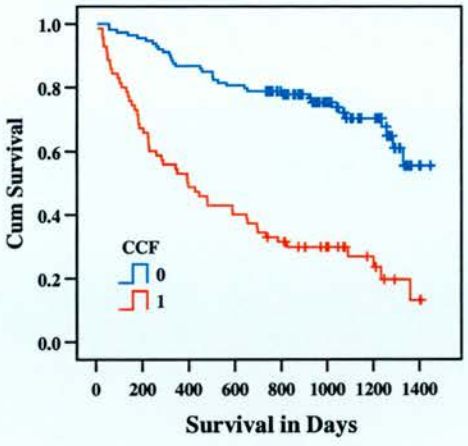

Figure 5.12; Survival curve for Congestive cardiac failure (p=0.0001)

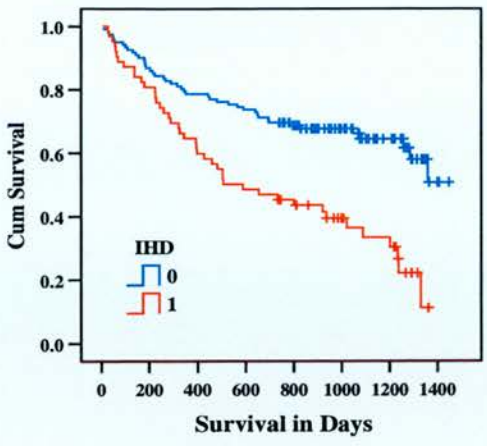

Figure 5.13; Survival curve for Ischaemic heart disease (p=0.0001)

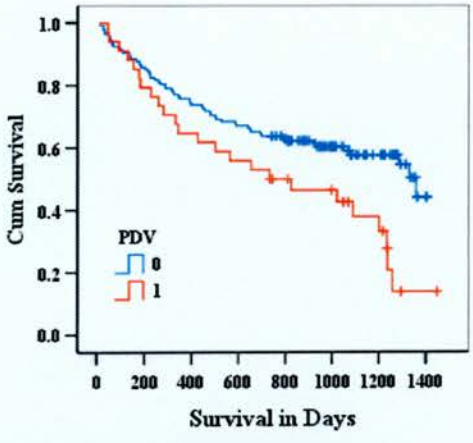

Figure 5.14; Survival curve for Peripheral vascular disease (p=0.008)

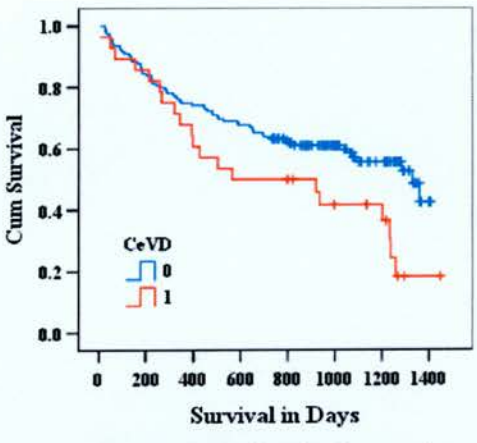

Figure 5.15; Survival curve for Cerebrovascular (p=0.02)

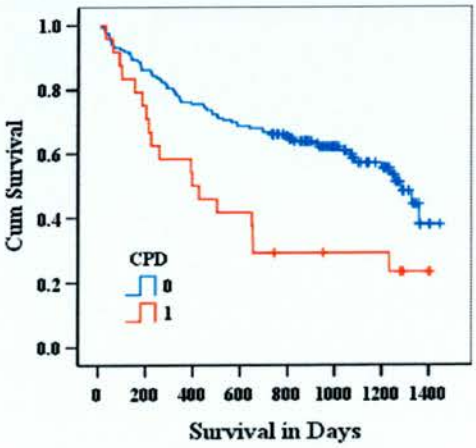

Figure 5.16; Survival curve for Chronic pulmonary disease (p=0.002)

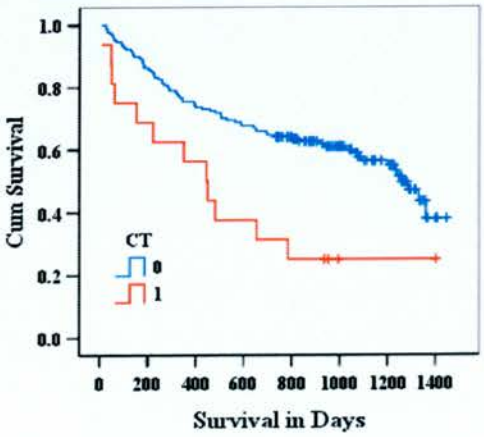

Figure 5.17; Survival curve for Connective tissue disease (p=0.003)

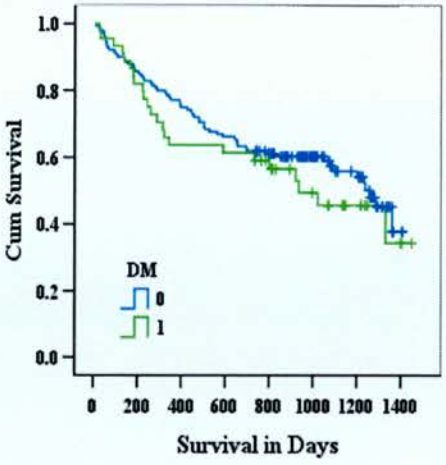

Figure 5.18; Survival curve for Diabetes mellitus (p=0.39)

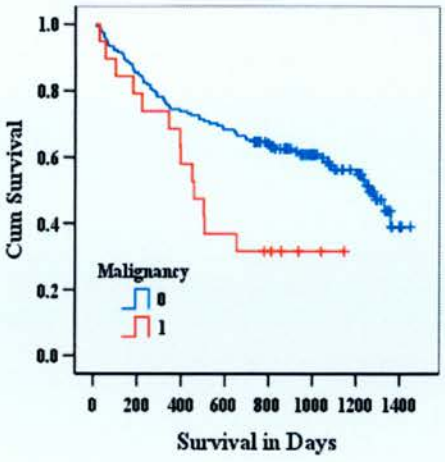

Figure 5.19; Survival curve for Malignancy (p=0.009)

5.7.5. Comorbidity Scores

Patients were grouped by comorbidity according to 3 different comorbidity scores to evaluate the effect of comorbid illnesses on patients' survival **(chapter 2)** (Khan score, Charlson index and Davies score).

5.7.5.1. Khan score

According to Khan score about half of all incident patients were categorized as high risk group (50.8%) with median age of 71 (64-78), the rest were assigned to low (20.2%) and medium (29%) risk groups respectively (**Table 5.13**).

Khan score	No	%	Median age	IQR
Low Risk	37	20.2	40	27-52
Medium Risk	53	29	65	48.5-74
High Risk	93	50.8	71	64-78

Table 5.13; Khan Score and risk groups

5.7.5.2 Charlson Comorbidity Index

Charlson scores were divided into 4 groups [which roughly represented quartiles]. The patients who scored from 3 to 7 on the total Charlson score were gathered into a CCI>2 group where as the other groups had given the same order of the total CCI score (**Table 5.14**).

CCI	No	%	Median age	IQR
CCI=0	43	23.5	43	34-63
CCI=1	39	21.3	63	42-74
CCI=2	34	18.6	69	57-80
CCI>2	67	36.6	70	64-76

Table 5.14; Charlson Index groups

5.7.5.3. Davies score

Davies scores were separated into 4 groups [which roughly represented quartiles] (**Table 5.15**). The group with comorbid conditions >2 included the oldest with the highest median age 71 years (65-77), in contrast the group of patients who started RRT with out any comorbid illness included the youngest group with median age 42 years (33-59).

Davies	No	%	Median age	IQR
0	47	25.7	42	33-59
1	48	26.2	63	51-74
2	42	23	70	57-78
>2	46	25.1	71	65-77

Table 5.15; Davies score groups

5.7.5.4. Comparison between the groups of comorbidity scores according to survival

Figures (5.20, 21, and 22) show the influence of comorbidity on survival. There was a significant difference in survival (p=0.0001) between the groups of all the 3 different scores. Patients with no comorbid illnesses (score zero/ low risk) had the lowest mortality rates with 8.1% in Khan, 10.6% in Davies score, and 14% in Charlson index. On the other hand the high risk group in Khan score and patients who scored >2 according to Charlson and Davies scores had the highest mortality rates 71% in Khan, 76.1% in Charlson, and 80.4% in Davies with median survival of 1.3, 1.1 and 0.9 years in Khan, Charlson and Davies score respectively **(Table 5.16)**.

Comorbidity scores	Number starting RRT	Number dead by 1/1/2007	% dead by 1/1/2007	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
Khan							0.0001
Low	37	3	8.1				
Medium	53	18	34				
High	93	66	71	1.3	0.7	1.9	
Charlson							0.0001
0	43	6	14				
1	39	11	28.2				
2	34	19	55.9	2.2	1	3.4	
>2	67	51	76.1	1.1	0.7	1.6	
Davies							0.0001
0	47	5	10.6				
1	48	17	35.4	3.7	3.1	4.2	
2	42	28	66.7	1.6	0.7	2.4	
>2	46	37	80.4	0.9	0.6	1.2	

Table 5.16; mortality difference between risk groups in different comorbidity scores

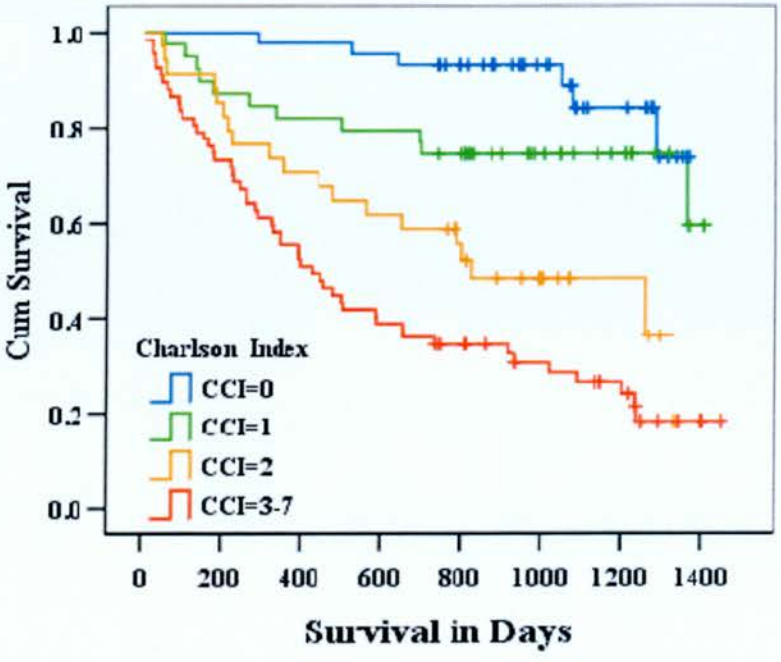

Figure 5.20; Survival by Charlson index groups

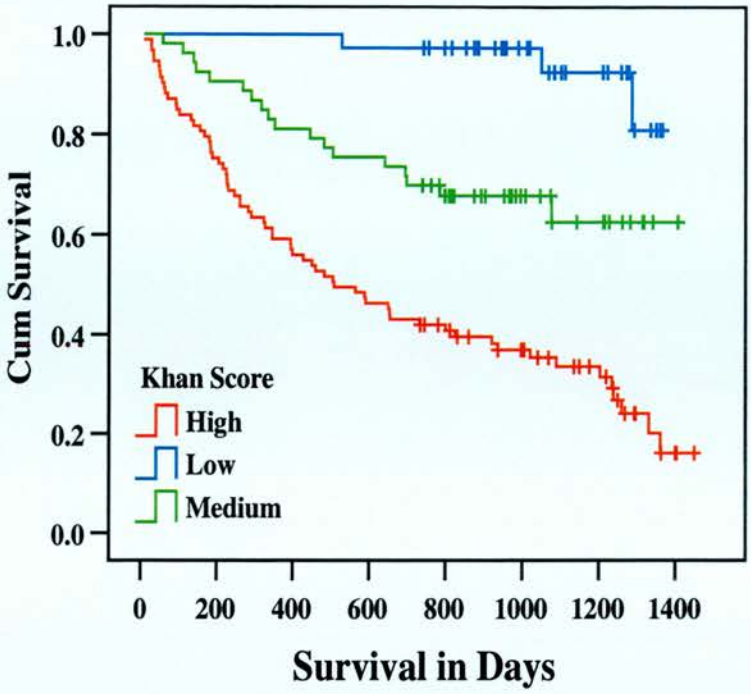

Figure 5.21; Survivals by Khan score groups

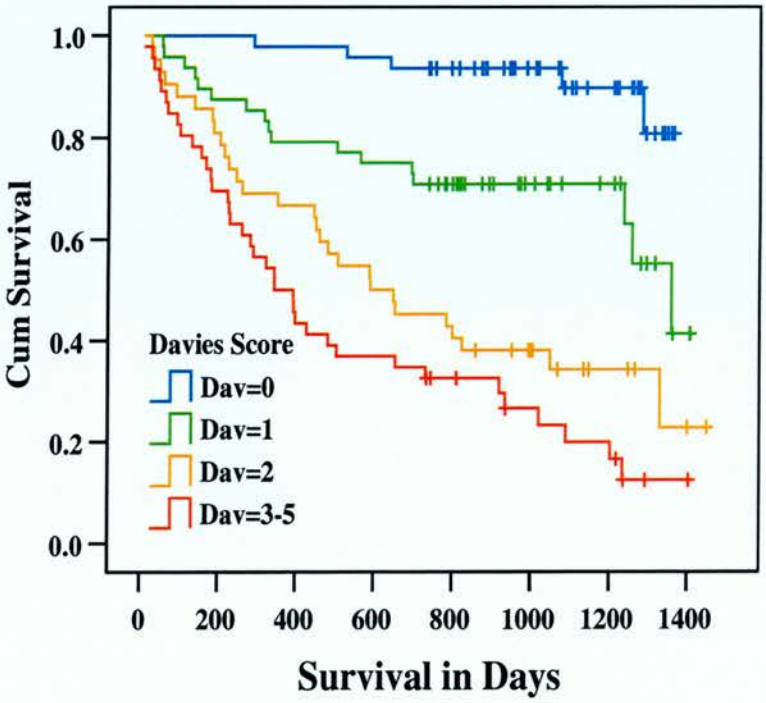

Figure 5.22; Survival by for Davies score groups

5.7.6. First RRT modality

Haemodialysis was the first modality of RRT in 85.2% of patients, peritoneal dialysis in 13.7% and pre-emptive transplant in 1.1% **(Figure 5.23)**.

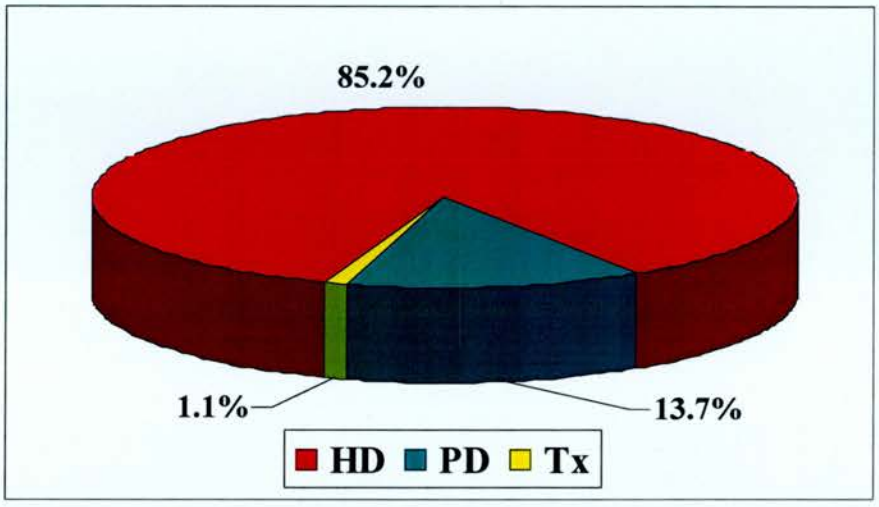

Figure 5.23; Percentage of first modality of RRT

5.7.6.1. Comparison between modality according to outcomes

The mortality difference between patients who started RTT on haemodialysis or peritoneal dialysis was significant (p=0.001) **(Figure 5.24).** More than half of haemodialysis patients died by the end of the study (53.8%) with median survival 2.9 years (1.9 – 3.9), in contrast mortality rate among peritoneal dialysis patients was 12% (median survival not reached) **(Table 5.17)**.

Modality	Number starting RRT	Number dead by 1/1/2007	% dead by 1/1/2007	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	0.001
Peritoneal dialysis	25	3	12				
haemodialysis	156	84	53.8	2.9	1.9	3.9	

Table 5.17; Mortality difference between peritoneal dialysis and haemodialysis patients

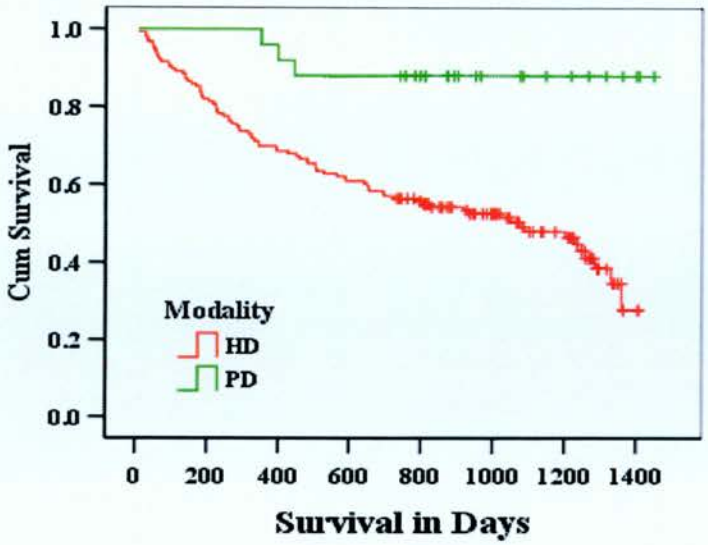

Figure 5.24; Survival curve according to modality of treatment (p=0.001)
HD=haemodialysis, PD=peritoneal dialysis

5.7.7. Vascular access

In the analysis, 49.2% of patients started RRT using definitive access. Of patients commencing on haemodialysis, 41% commenced with definitive access. Of those known early to the renal unit more than half started haemodialysis with definitive access (57.4% and 58.8% for 3 months and 6 months respectively) **(Figure 5.25)**. Haemodialysis patients who started dialysis with permanent access were younger with median age 62 years (42-74), while those who started with temporary access had a median age of 70 years (59-77).

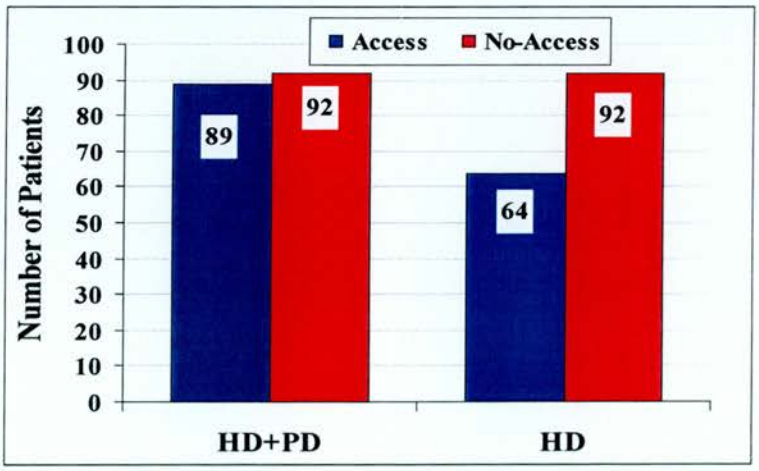

Figure 5.25; Number of patients started with and without permanent access in haemodialysis and peritoneal dialysis (HD+PD) and in haemodialysis (HD) patient only

5.7.7.1. Comparison between access groups according to survival

Univariate analysis of the outcome according to access showed a significant difference in mortality in all patients (haemodialysis and peritoneal dialysis patients but excluding those who started RRT with pre-emptive kidney transplant) (**Table 5.18**). Patients who started dialysis with temporary access had increased risk of death by 2.4 times higher than those who started RRT with permanent access (76.3%vs.28%) at median follow up time 817 days (**Figure 5.26**). Univariate analysis including only haemodialysis patients (**Figure 5.27**) showed that mortality risk was 1.9 times higher in haemodialysis patient who started with temporary access compared with patients who started with permanent access (67.3%vs.34.3%).

Access	Number starting RRT	Number dead by 1/1/2007	% dead by 1/1/2007	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
Haemodialysis + peritoneal dialysis							0.0001
Access	89	25	28				
No access	92	62	67.3	1.3	0.6	2.1	
haemodialysis							0.0001
Access	64	22	34.3	3.7	3.2	4.1	
No access	92	62	67.3	1.3	0.5	2.1	

Table 5.18; Mortality difference between patients started with and without permanent access.

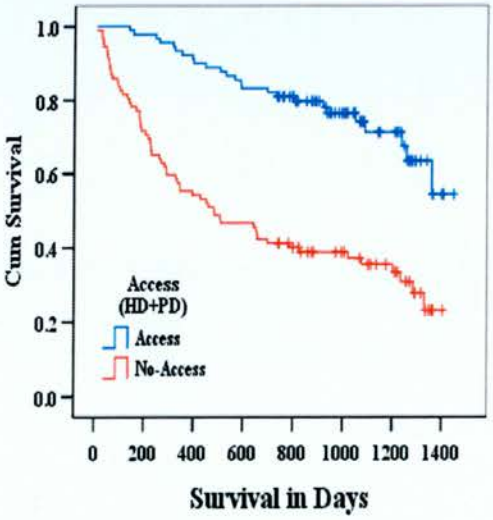

Figure 5.26; Survival curve according to access in Haemodialysis and peritoneal dialysis patients (p=0.0001)

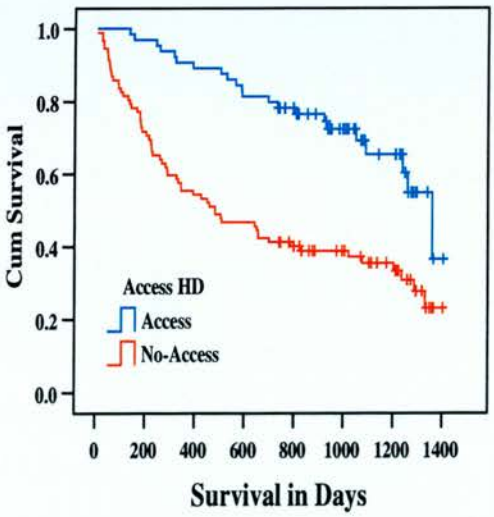

Figure 5.27; Survival curve according to access in haemodialysis patients only (p=0.0001)

5.7.8. Referral

Referral time was calculated as the number of days between the first recorded biochemical result and the date of initiation of RRT. Referral times of 90 days or more were considered as early referral. Referral times less than 90 days were defined as late referral. Another consideration in the same way was done for a period of 6 months.

Most patients had been known to the renal unit before starting dialysis (72.1% for over 3 months and 68.3% for over 6 months) **(Figure 5.28)**. Patients referred late were older than patients referred earlier **(Figure 5.29)**.

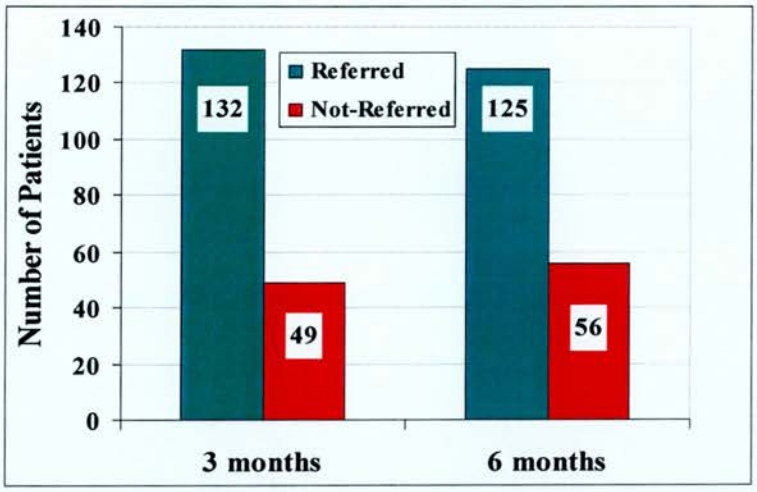

Figure 5.28; Number of patients referred and not-referred at starting of RRT (3 and 6 months)

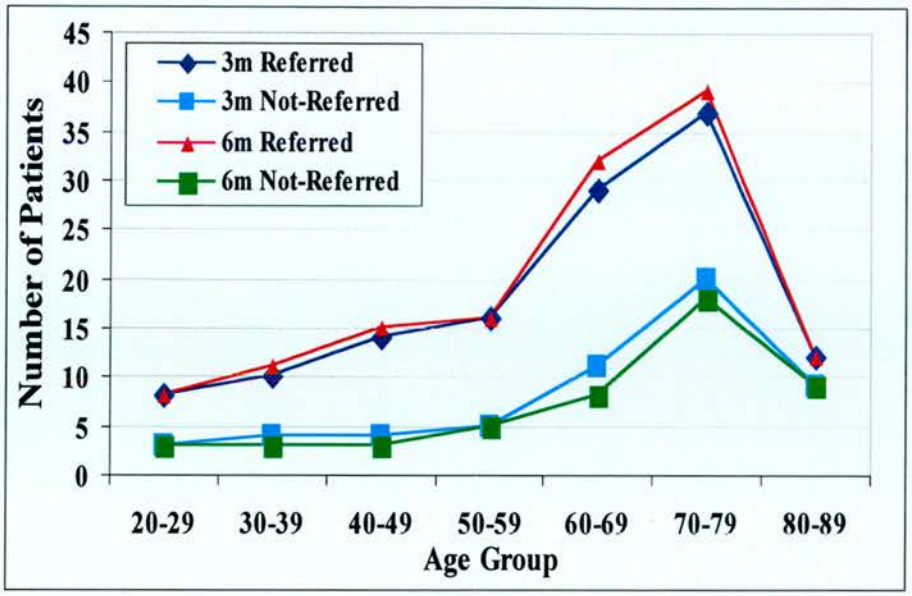

Figure 5.29; Age group in 10 years and referral to renal unit in 3 and 6 months

5.7.8.1. Comparison between referred groups according to outcome

Univariate analysis demonstrated a significant difference in survival between patients who had or had not been referred to the renal unit at least 3 months (p=0.034) or 6 months (p=0.050) prior to starting dialysis (**Table 5.19**). The mortality rates of referred patients were 43.1 % and 43.2% (median survival of 3.4 and 3.7 years) for 3 months and 6 months respectively. On the other hand the mortality rates for not-referred patients were 61.2% for 3 months with median survival 1.9 year and 58.9% for 6 months with median survival 2.1 years **(Figures 5.30 and 5.31).**

Referred groups	Number starting RRT	Number dead by 1/1/2007	% dead by 1/1/2007	Median survival (years)	95% CI for median survival (years)		Log rank p-value
					lower	upper	
3 months							0.034
Referred	132	57	43.1	3.4	2.8	4	
Not-Referred	49	30	61.2	1.9	1.2	2.5	
6 months							0.050
Referred	125	54	43.2	3.7	2.7	4	
Not-Referred	56	33	58.9	2.1	0.3	3.9	

Table 5.19; Mortality difference between referred or not-referred patients in 3 and 6 months

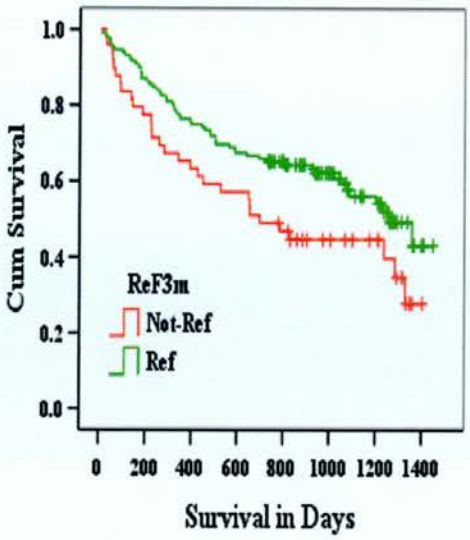

Figure 5.30; Survival curve for referral at 3 months (p=0.034)

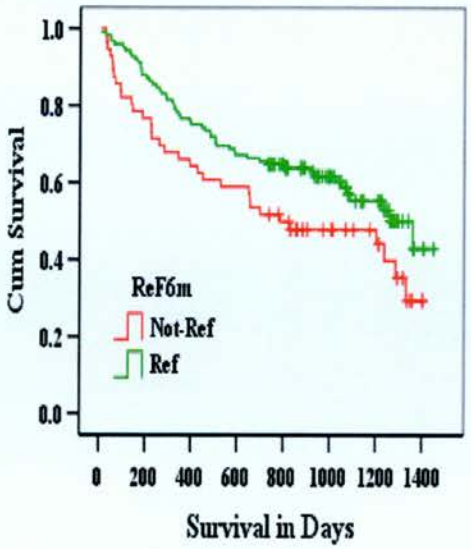

Figure 5.31; Survival curve for referral at 6months (p=0.050)

5.8. Comparison between patient in the first year, second year and at end of the study including and excluding 90 days mortality according to outcome

Univariate analysis of the patients in the first year, second year and at end of the study (median follow up 817 days) including 90 days mortality showed that age, comorbidity risk groups based on the 3 different comorbidity scores, initial access for RRT, initial mode of RRT, initial serum albumin, initial serum cholesterol, and initial CRP were all significantly associated with death within first year, second year and at end of the study (**Table 5.20, 5.21 and 5.22**). The same univariate analysis was repeated excluding those patients who died within the first 90 days revealed that the same factors listed above were significantly associated with patient mortality.

Referral to dialysis at 3 months was associated with mortality at 2 years and at the end of the study when first 90 days mortality was included. Referral at 6 months and primary renal diagnosis were only significantly associated with mortality at the end of the study (1/1/2007) if 90 days dead patients were included. Patients with primary renal diagnoses of interstitial nephritis, multisystem disease, diabetic nephropathy, and unknown cause of ESRD had worse survival than the reference glomerulonephritis group. However, the highest mortality rate was among

multisystem disease group 34.5%, while the best survival was among glomerulonephritis and interstitial nephritis 25% **(Table 5.22).**

Univariate analysis of all coexisting illnesses at start of RRT when 90 days mortality was included (**Table 5.20, 5.21 and 5.22**) revealed that congestive cardiac failure and ischaemic heart disease were significantly associated with death in first year, second year and at end of the study. Chronic pulmonary diseases and connective tissue disease were significantly associated with mortality at second year and at end of the study. Malignancy associated with mortality at two years whereas, peripheral vascular disease at end of the study.

Patients' sex did not influence survival, nor did haemoglobin concentration, eGFR, or urea concentration at time of initiating RRT.

5.8.1. One year patient characteristics and univariate analysis

	Cohort n=183	1year survivors n=135	Dead by 1 year n=48	p value & statistic test
Median age (years) (IQR)	65 (18-88)	62 (44-74)	71 (64-78)	p=0.0001 M-W
Age≥65 years	97 (52.7)	63 (46.7)	34 (70.8)	p=0.004 χ^2
Permanent access (HD+PD)	89 (49.2)	82 (61.7)	7(14.6)	p=0.022 χ^2
Access HD	64 (41)	58 (53.2)	6 (12.8)	
First Mode of RRT				p=0.006 χ^2
Haemodialysis	156 (86.2)	109 (69.9)	47 (30.1)	
Peritoneal dialysis	25 (13.8)	24 (96)	1 (4)	
Mean Albumin (g/l)	33.6 SD 5.5	34.6 SD 5.5	30.7 SD 4.5	p=0.008 T-test
Mean cholesterol (mmol/l)	4.5 SD 1.2	4.6 SD 1.2	3.9 SD 1.1	p=0.002 T-test
Median CRP (mg/l) (IQR)	15 (5-49)	9 (5-35)	36 (18-106)	p= .001 M-W
Comorbid Conditions				
Congestive cardiac failure	70 (38.3)	37 (27.4)	33 (68.8)	p=0.0001 χ^2
Ischaemic heart disease	62 (33.9)	40 (29.6)	22 (45.8)	p=0.0001 χ^2
Khan Score				p=0.0001 χ^2
Low	37 (27.4)	37 (27.4)	0	
Medium	53 (29)	43 (31.9)	10 (20.8)	
High	93 (50.8)	55 (40.7)	38 (79.2)	
Charlson Index				p=0.0001 χ^2
CCI=0	43 (23.5)	42 (31.1)	1 (2.1)	
CCI=1	39 (21.3)	32 (23.7)	7 (14.6)	
CCI=2	34 (18.6)	24 (17.8)	10 (20.8)	
CCI=3-7	67 (36.6)	37 (27.4)	30 (62.5)	
Davies Score				p=0.0001 χ^2
Davies=0	47 (25.7)	46 (34.1)	1 (2.1)	
Davies=1	48 (26.2)	38 (28.1)	10 (20.8)	
Davies=2	42 (23)	28 (20.7)	14 (29.2)	
Davies=3-5	46 (25.1)	23 (17)	23 (47.9)	

Table 5.20; Patient characteristics and univariate analysis of factors affecting mortality at 1 year, M-W=Mann-Whitney Test, χ^2 = Chi square, IQR= inter-quartile range,

5.8.2. Two years patient characteristics and univariate analysis

	Cohort n=183	2 year survivors n=113	Dead by 2year n=70	p value & statistic test
Median age (years) (IQR)	65 (50-75)	59 (42-71)	71 (64-78)	p=0.0001 M-W
Age≥65 years	97 (53)	49 (43.3)	48 (68.6)	p=0.0001 χ^2
Referred 3 m	132 (72.9)	86 (78.2)	46 (64.8)	p=0.048 χ^2
Referred 6 m	125 (69.1)	81 (73.6)	44 (62)	p=0.097 χ^2
Permanent access (haemodialysis and peritoneal dialysis)	89 (49.2)	72 (65.5)	17 (23.9)	p=0.0001 χ^2
Access haemodialysis	64 (41)	50 (56.8)	14 (20.6)	p=0.0001 χ^2
First Mode of RRT				p=0.003 χ^2
haemodialysis	156 (86.2)	88 (80)	84 (95.8)	
Peritoneal dialysis	25 (13.8)	22 (20)	3 (4.2)	
Mean Albumin (g/l)	33.6	35.3	30.9	p=0.0001 T-test
Mean cholesterol (mmol/l)	4.5	4.6	4.1	p=0.003 T-test
Median CRP (mg/l) (IQR)	15 (5-49)	7 (4-22)	34 (15-97)	p= 0.0001 M-W
Comorbid Conditions				
Congestive cardiac failure	70 (38.3)	24 (21.4)	46 (64.8)	p=0.001 χ^2
Ischaemic heart disease	62 (33.9)	28 (25)	34 (47.9)	p=0.0001 χ^2
Malignancy	19 (10.4)	6 (5.4)	13 (18.3)	p=0.005 χ^2
Chronic pulmonary disease	24 (13.1)	7 (6.3)	17 (23.9)	p=0.001 χ^2
Connective tissue disease	16 (8.7)	5 (4.5)	11 (15.5)	p=0.021 χ^2
Comorbidity				p=0.0001 χ^2
Low	56 (30.6)	48 (42.5)	8 (11.4)	
Medium	52 (28.4)	32 (28.3)	20 (28.6)	
High	75 (41)	33 (29.2)	42 (60)	

Table 5.21; Patient characteristics and univariate analysis of factors affecting mortality at 2.years M-W=Mann-Whitney Test, χ^2 = Chi square, IQR= inter-quartile range,

5.8.3. Patients characteristics and univariate analysis at end of the study

	Cohort n=183	Survivors by 1/1/2007 n=96	Dead by 1/1/2007 n=87	p value & statistic test
Median age (years) (IQR)	65 (50-75)	55 (40-68)	72 (64-78)	p=0.0001 M-W
Age≥65 years	97 (53)	34 (35.4)	63 (72.4)	p=0.0001 χ^2
Referred 3 m	132 (72.9)	75 (56.8)	57 (43.2)	p=0.031 χ^2
Referred 6 m	125 (69.1)	71 (56.8)	54 (43.2)	p=0.050 χ^2
Permanent access (HD+PD)	89 (49.2)	64 (68.1)	25 (28.7)	p=0.0001 χ^2
Access haemodialysis	64 (41)	42 (58.3)	22 (26.2)	p=0.0001 χ^2
First Mode of RRT				p=0.0001 χ^2
Haemodialysis	156 (86.2)	72 (46.2)	84 (53.8)	
Peritoneal dialysis	25 (13.8)	22 (88)	3 (12)	
Primary renal diagnosis				p=0.024 χ^2
Glomerulonephritis	41 (22.4)	24 (25)	17 (19.5)	
Interstitial Nephritis	34 (18.6)	24 (25)	10 (11.5)	
Multisystem disease	52 (28.4)	22 (22.9)	30 (34.5)	
Diabetic nephropathy	19 (10.4)	12 (12.5)	7 (8)	
Unknown	37 (20.2)	14 (14.6)	23 (26.4)	
Mean Albumin (g/l)	33.6	35.5	31.5	p=0.0001 T-test
Mean cholesterol (mmol/l)	4.5	4.7	4	p=0.0001 T-test
Median CRP (mg/l) (IQR)	15 (5-49)	8 (4-19)	31 (8-82)	p= 0.0001 M-W
Comorbid Conditions				
Congestive cardiac failure	70 (38.3)	17 (17.7)	53 (60.9)	p=0.0001 χ^2
Ischaemic heart disease	62 (33.9)	19 (19.8)	43 (49.4)	p=0.0001 χ^2
Cerebrovascular disease	28 (15.3)	8 (8.3)	20 (23)	p=0.006 χ^2
Peripheral vascular disease	34 (18.6)	10 (10.4)	24 (27.6)	p=0.003 χ^2
Chronic pulmonary disease	24 (13.1)	6 (6.3)	18 (20.7)	p=0.004 χ^2
Connective tissue disease	16 (8.7)	4 (4.2)	12 (13.8)	p=0.021 χ^2
Khan Score				p=0.0001 χ^2
Low	37 (20.2)	34 (35.4)	3 (3.4)	
Medium	53 (29)	35 (36.5)	18 (20.7)	
High	93 (50.8)	27 (28.1)	66 (75.9)	
Charlson Index				p=0.0001 χ^2
CCI=0	43 (23.5)	37 (38.5)	6 (6.9)	
CCI=1	39 (21.3)	28 (29.2)	11 (12.6)	
CCI=2	34 (18.6)	15 (15.6)	19 (21.8)	
CCI=3-7	67 (36.6)	16 (16.7)	51 (58.6)	
Davies Score				p=0.0001 χ^2
Davies=0	47 (25.7)	42 (43.8)	5 (5.7)	
Davies=1	48 (26.2)	31 (32.3)	17 (19.5)	
Davies=2	42 (23)	14 (14.6)	28 (32.2)	
Davies=3-5	46 (25.1)	9 (9.4)	37 (42.5)	

Table 5.22; Patient characteristics and univariate analysis of factors affecting mortality at end of the study, M-W=Mann-Whitney Test, χ^2 = Chi square, IQR= inter-quartile range.

5.9. Multivariate analysis of patient mortality

The Cox regression model of survival analysis was used to identify independent factors associated with death at the end of the study (median 817 days of follow up). Firstly, including patients who died within 90 days, therefore survival analysis was performed for 183 patients. Secondly, excluding those who died within the first 90 days of starting dialysis, survival analysis involved 170 patients.

The same analysis was done 4 times, because every analysis was performed using a different comorbidity score (Charlson index, Khan Score, Davies score, and all comorbid illnesses). All showed common results regarding initial serum cholesterol, initial access for RRT, and age at start of RRT except for the Khan model as Khan score depends on age.

The variables used in the multivariate analysis were age (except when Khan score used), gender, referred in 3 months and 6 months periods, first mode of RRT, access at initiation of RRT (haemodialysis and peritoneal dialysis), initial serum-haemoglobin, albumin, cholesterol, CRP, and also eGFR, primary renal diagnosis, and one of the comorbidity scores. The main outcome was 2 years patient survival with binary description (1= death, 0 = live). Gender, referral to nephrology care, access, and modality were also binary variables.

5.9.1. Charlson Index

In this analysis Charlson scores were divided into 4 groups to provide more statistical power. Initial access for RRT was most significant factor; patients who started dialysis with no permanent access had an increased risk of death by 2.9 times greater than those who started dialysis with permanent access (for haemodialysis and peritoneal dialysis). The initial serum cholesterol had a beneficial effect upon survival; each 1mmol/l increase in serum cholesterol decreased the hazard of death by 19%. Each additional year of patient age increased their chance of death by 3%. The increase in Charlson score increased the odds of death, those scored 1 had 2.1 times increase in hazard of death compared with reference group with Charlson score

of zero, this hazard increase to 3.4 times for those who scored 2 and over 5 times to those who scored >2 (**Table 5.23).**

The analysis excluding those who died with in the first 90 days showed that each additional year of patient age increased the risk of death by 2%, and patients who started dialysis with temporary access had an increased hazard of death of 2.9% from those who started RRT on permanent access. Patients not referred to nephrology care at least 6 months before starting dialysis had increased hazard of death of 1.8 times greater than those who had been referred. Charlson score, those who score 1 had 1.8 times increased odds of death from those who scored zero, that risk increased to 3.5 in those who scored 2 and 5.3 in those who scored >2 (**Table 5.24**).

Other variables analysed which did not contribute significantly to the multivariate model were gender, first mode of RRT, serum albumin, GFR, haemoglobin, CRP, and primary renal diagnosis.

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Age (years)	0.009	1.03	1.01	1.05
Access	0.0001	2.92	1.81	4.71
Cholesterol (mmol/l)	0.043	0.81	0.66	0.99
Charlson index				
0	0.001	Ref	-	
1		2.1	0.75	5.85
2		3.42	1.28	9.15
>2		5.2	2.11	12.86

Table 5.23; Cox regression survival analysis Charlson Index model

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Age (years)	0.014	1.02	1.01	1.04
Access	0.0001	3.40	1.93	5.98
Referral after 6 months	0.031	1.86	1.05	3.26
Charlson index				
0	0.000	Ref	-	
1		1.85	0.65	5.26
2		3.58	1.30	9.86
>2		5.31	2.12	13.31

Table 5.24; Cox regression survival analysis Charlson Index model excluding 90 days death

5.9.2. Khan Score

Khan score stratifies patients into three risk groups (Low, medium and high) according to comorbidity and age. The analysis using the Khan score showed that factors associated with mortality were the same as when the Charlson index was used. The only difference was the increased risk of death among Khan high risk groups. The Khan score showed that odds of death are significantly increased by 6.5 times and over 13 times in the medium and high risk groups respectively, compared with the low risk group (**Table 5.25).**

When those patients who died in the first 90 days were excluded, the analysis showed the same results of Charlson score but with higher risk of death among Khan Risk groups. Risk of death increased the by 6.5 times and 13.9 times in medium and high risk groups respectively compared to the low risk group. Moreover, using Khan score showed that Patients who started treatment on haemodialysis had a 3.5 greater risk of death than those who started on peritoneal dialysis (**Table 5.26**).

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Access	0.0001	3.33	2.08	5.35
Cholesterol (mmol/l)	0.004	0.75	0.61	0.91
Khan score				
Low risk group	0.0001	Ref	-	
Medium risk group		6.57	1.92	22.53
High risk group		13.17	4.11	42.17

Table 5.25; Cox regression survival analysis Khan score model.

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Access	0.0001	3.30	1.85	5.88
Referral at 6 months	0.008	2.14	1.21	3.77
Modality	0.041	3.54	1.05	11.93
Khan score				
Low risk group	0.0001	Ref	-	
Medium risk group		6.59	1.90	22.78
High risk group		13.96	4.31	45.26

Table 5.26; Cox regression survival analysis Khan score model excluding 90 days death

5.9.3. Davies score

In this analysis Davies scores were divided into 4 groups to provide more statistical power. The Davies score showed the same results when Charlson index used, but the risk of death was higher among Davies higher risk groups. Those who scored 1 had 3.9 times greater hazard of death compared with those with a Davies score of zero. This hazard increased to 5.6 times for those who scored 2 and to 7.4 times to those who scored >2 (**Table 5.27).**

When those who died in the first 90 days were excluded again the analysis showed the same results as the Charlson model but the risk of death was higher among Davies high risk groups. Risk of death increased by 4.8, 9.2 and 12.3 times higher in patients with scores 1, 2 and >2 respectively compared to those who score zero. In addition, patients who started on haemodialysis had a risk of death 3.6 greater than peritoneal dialysis. Also each 1mg/l increase in CRP increased the hazard of death by 1% (**Table 5.28**).

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Age (years)	0.03	1.02	1.02	1.04
Access	0.0001	2.95	1.81	4.83
Cholesterol (mmol/l)	0.016	0.77	0.63	0.95
Davies Score				
0	0.001	Ref	-	
1		3.96	1.39	11.34
2		5.60	2.01	15.66
>2		7.47	2.74	20.41

Table 5.27; Cox regression survival analysis Davies score model

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Access	0.002	2.62	1.44	4.77
Modality	0.039	3.60	1.06	12.21
CRP (mg/l)	0.029	1.01	1	1.02
Referral at 6 months	0.006	2.34	1.27	4.31
Davies Score				
0	0.001	Ref	-	
1		4.82	1.71	13.56
2		9.22	3.45	24.66
>2		12.36	2.74	32.27

Table 5.28; Cox regression survival analysis Davies score model excluding 90 days death

5.9.4. Comorbid conditions

In this analysis all the comorbid conditions that have been collected at the start of dialysis were entered as independent factors instead of using a standard comorbidity score. The analysis revealed that congestive cardiac failure as a comorbid disease increased the odds of death by 2.5 times greater than those who started without congestive cardiac failure. Also serum albumin had a beneficial effect upon survival; each 1mg/l increase in serum albumin decreases the hazard of death by 4%. Patients who were not referred at 6 months before starting dialysis had an increased risk of death of 1.9 times than those who referred (**Table 5.29).**

Excluding patients who died in the first 90 days, the analysis showed the same results as the analysis including 90 days patients except that ischaemic heart disease now reached significance, increasing the hazard of death by 2.6 times greater in patients started dialysis with ischaemic heart disease from those who started RRT without ischaemic heart disease (**Table 5.30).** Cholesterol was no longer an independent risk factor predicting mortality. Furthermore, higher serum albumin levels now were associated with decreased mortality.

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Age (years)	0.0001	1.03	1.01	1.05
Access	0.0001	1.93	1.13	3.32
Cholesterol (mmol/l)	0.017	0.79	0.64	0.96
Albumin (g/l)	0.050	0.96	0.92	1.00
Referral 6 months	0.016	1.93	1.12	3.32
Congestive cardiac failure	0.0001	2.59	1.63	4.12

Table 5.29; Cox regression survival analysis all comorbid conditions model

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Age (years)	0.002	1.02	1.01	1.04
Access	0.0001	2.89	1.63	5.10
Referral in < 6 months	0.0001	2.84	1.55	5.21
Albumin (g/l)	0.002	1.02	1.01	1.04
Ischemic heart disease	0.048	1.62	1.01	2.62
Congestive cardiac failure	0.0001	2.48	1.52	4.05

Table 5.30; Cox regression survival analysis all comorbid conditions model excluding 90 days death

5.10. Hospitalisation

Hospitalization is a common occurrence in haemodialysis patients and the data on hospitalisation for RRT patients are potentially informative about disease burden to those patients and health services.

Patients with established renal disease are potentially subject to frequent hospital admission during the course of their illness. This can be well seen in this study as the number of patients who were not admitted to hospital in a period of two years was only 13 (7.1%) **(Figure 5.32)**. The maximum number of days spent in hospital was 497 days by one patient who died after he spent 650 days on RRT, meaning he had spent 73.6% of his treatment time in hospital.

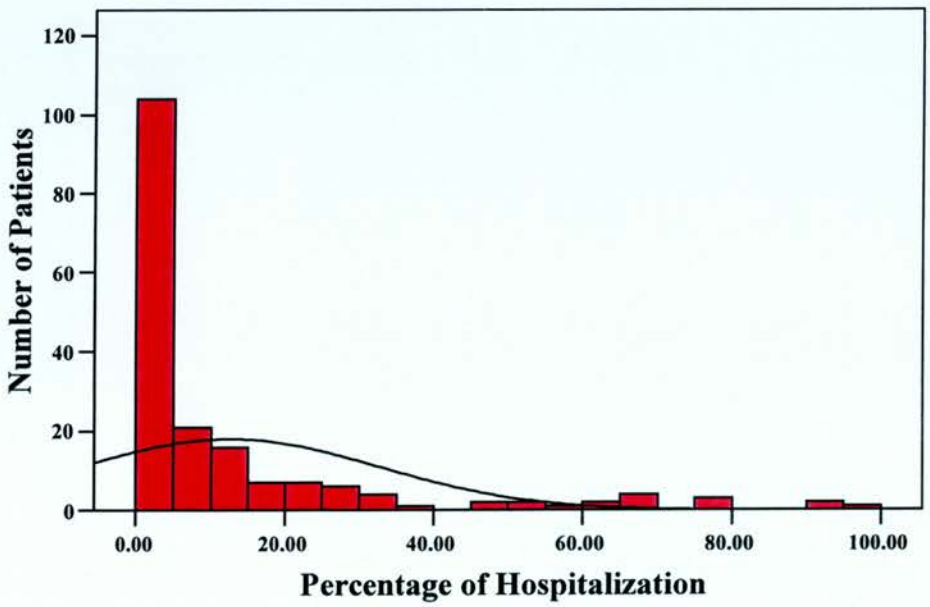

Figure 5.32; Histogram of hospitalisation percentage of patients who started RRT in 2003 and 2004

5.10.1. Correlation of hospitalisation and continuous variables

Using Pearson Correlation to find any correlation between numbers of days spent in hospital and other continuous variables (age, eGFR, albumin, CRP, cholesterol, Hb, and urea) revealed similar associations as with mortality. The number of days spent in hospital was significantly associated with age, CRP, and serum albumin. The association with age and CRP was direct correlation (as age and CRP level increased the number of days spent in hospital increased). However, with initial serum albumin there was an inverse correlation (as serum albumin was low at the start of RRT the days spent in hospital increased) **(Table 5.31)**.

	Age	Serum albumin	CRP
Days spent in hospital			
Pearson Correlation	0.265	- 0.326	0.332
p-value	0.0001	0.0001	0.0001

Table 5.31; Pearson Correlations of hospitalisation

5.10.2. Comparison between groups according to percentage of time spent in hospital

The percentage of time at risk (time from starting of RRT to either death or exactly two years) spent in hospital was calculated for each patient as has been explained in chapter 2. Kruskal Wallis test used to compare the groups (p-value<0.05 was significant). The median percentage of time spent in hospital for all patients was 4.1% (0.9% – 13.9%) (Mean = 12.5%) and was dropped to 3.4 (0.7% - 10.7%) when 90 days mortality excluded (Mean = 9.3%).

Results showed that the percentage of time at risk spent in hospital was highest for patients age ≥65 years. There was a significant difference in percentage of time at risk spent in hospital between risk groups (as the comorbidity burden increased the time spent in hospital was markedly increased) **(Table 5.32)**.

	Cases no	Cases %	Median % time spent in hospital	IQR	Kruskal-Wallis Test (p-value)
Age group					0.0001
<65 years	86	47	2.8	0.8 – 5.4	
≥65 years	97	53	9.5	1.7 – 24.7	
Charlson index					0.005
CCI=0	43	23.5	2.3	0.8 – 4.3	
CCI=1	39	21.3	2.4	0.6 – 5.4	
CCI=2	34	18.6	7.8	0.9 – 19.4	
CCI>2	67	36.6	10	2.8 – 25.4	
Khan score					0.0001
Low	37	20.2	1.5	0.4 – 3.4	
Medium	53	29	3.2	0.8 – 8.7	
High	93	50.8	9.9	2.4 – 25.9	

Table 5.32; hospitalisation percentage according to age and comorbidity

The percentage of time spent in hospital was significantly higher in female than male (5.3% vs. 3%), and in haemodialysis patients compared with peritoneal patients (4.3% vs. 1.9%). The analysis showed that patient who started RRT without permanent access had a greater median percentage of time at risk spent in hospital than those patients who started RRT with definitive access (11% vs. 1.5). The percentage of time spent in hospital was highest for patients not-referred early to nephrology care (**Table 5.33**).

	Cases no	Cases %	Median % time spent in hospital	IQR	Kruskal-Wallis Test (p-value)
Gender					0.002
Male	100	55	3	0.6 – 10	
Female	83	45	5.3	2 – 20.2	
First modality treatment					0.006
Peritoneal dialysis	25	13.8	1.9	0.6 – 4.6	
Haemodialysis	156	86.2	4.3	1.5 – 15.7	
Initial access (HD+PD)					0.0001
Access	89	49.2	1.5	0.5 – 4.1	
No access	92	50.8	11	3.5 – 28.8	
Referral 3 months					0.0001
Referred	132	72.9	3.2	0.8 – 10	
Not-referred	51	27.1	10.5	3.2 – 10	
Referral 6 months					0.0001
Referred	125	69.1	2.8	0.8 – 10	
Not-referred	58	30.9	9.4	3.2 – 30.2	

Table 5.33; Hospitalisation percentage according to gender, modality, access and referral

The median percentage of time spent in hospital was not significant by different according to primary renal disease (**Table 5.34**).

	Cases no	Cases %	Median % time spent in hospital	IQR	Kruskal-Wallis Test (p-value)
Primary renal diagnosis					0.273
Glomerulonephritis	41	22.2	3.2	1 – 14.9	
Interstitial nephritis	34	18.6	3.4	0.7 – 6	
Multisystem disease	52	28.4	4.7	1.5 – 15.1	
Diabetic nephropathy	19	10.4	2.2	0.4 – 9.3	
Unknown	37	20.2	4.7	1.7 – 21.3	

Table 5.34; Hospitalisation percentage according to primary renal diagnosis groups

5.11. Summary

The gross mortality of this incident RRT cohort was 26.2% at one year 38.2% at two years and 47.5% at the end of the study. When deaths within the first 90 days of treatment were excluded these mortality rates were 20.6%, 33.5% and 43.5% respectively. The most common cause of mortality was cardiovascular disease (40.7%) followed by infection (29.1%).

Univariate analysis of the first year, two years and at the end of the study including and excluding 90 days mortality revealed that age, comorbidity, starting RRT with definitive access, first treatment modality, initial serum albumin, initial serum cholesterol and CRP were all associated with mortality.

Multivariate analysis with different comorbidity scores showed that age (except when Khan score was used), comorbidity, initial access, initial serum cholesterol were significantly associated with death. When the same analysis was carried out with exclusion of those who died in the first 90 days initial serum cholesterol was no longer significantly associated with death. However, no referral to renal unit at least 6 months prior starting dialysis was significantly associated with death in addition to age, comorbidity, and initial access.

Congestive cardiac failure and ischaemic heart disease were significant risk factors for mortality when those patients who died within the first 90 days were included and excluded.

Hospitalisation percentage was higher in more elderly patients, high co-morbidity risk groups, female patients, patients started dialysis without access, haemodialysis patients, and in patients who were not referred early.

This study has emphasized that age, comorbidity, initial access, initial serum cholesterol were associated with survival of 2003 and 2004 patients receiving RRT in RIE renal unit.

5.12. Mortality of patients treated by haemodialysis

156 patients started RRT on haemodialysis with median age 65 years (IQR 54 to 76). They had more comorbid conditions compared to 25 patients who started RRT on peritoneal dialysis, who were also younger (median age 53 years and IQR 42 to 67). Accordingly survival of haemodialysis patients will be analyzed separately in this section.

5.12.1. Patient mortality

Of the 156 patients, 47 (30.1%) were dead by the end of one year 84 (53.8%) by the end of the study. In order to make these figures more directly comparable with the USRDS, 13 death within the first 90 days of RRT were excluded and the mortality at the end of one year was 34 patients (23.8%) and 71 patients (49.7%) by the end of the study (**Table 5.35).**

Duration of RRT	**Overall Mortality n=156**		**Excluding 90days deaths n=143**	
	n	%	n	%
90days	13	8.3%	-	-
6month	25	16%	12	8.4%
1year	47	30.1%	34	23.8%
18months	58	37.2%	45	31.5%
2 years	67	42.9%	54	37.8%
End of study	84	53.8%	71	49.7%

Table 5.35; Mortality of haemodialysis patients receiving RRT

5.12.2. Causes of death

Infection was the leading cause of death in the first year 37%, followed by cardiovascular 34.8%, others 21.7%, unknown 4.3% and malignancy 2.1%. At the end of the study cardiovascular disease was the main cause of death 41%, followed by infection 27.9%, others 16.9% unknown cause 9.6%, malignancy 4.8 % **(Table 5.36)**.

Cause of death	One year		End of the study	
	n	%	n	%
Cardiovascular	16	34.8	34	41
Infection	17	37	23	27.9
Malignancy	1	2.2	4	4.8
Unknown	2	4.3	8	9.6
Others	10	21.7	14	16.9

Table 5.36; Cause of death including those who died in the first 90 days in haemodialysis patients at one year and at end of the study

5.12.3. Comparison between patient including and excluding 90 days mortality according to outcome at end of the study

Univariate analysis between survivors and dead haemodialysis patients including those who died in the first 90 days revealed a significant difference in the following data: age (those who survived to the end of the study were younger, median age 56 years), patients who started dialysis through permanent access showed better survival (65.5%), patients who started haemodialysis with no comorbid conditions (Khan=low, CCI=0 & Davies=0) are mainly survivors and as the comorbidity burden increased the proportion of survivors decreased. Congestive cardiac failure, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease and chronic pulmonary disease all showed a significant difference in survival. Survivors had higher initial serum albumin (35.2 ± 5.4), initial serum cholesterol (4.5 ±1.1), and lower levels of serum CRP (8mg/l). Primary renal diagnosis, gender and diabetes did not show significant effect on survival of haemodialysis

Univariate analysis of haemodialysis patients excluding those who started dialysis at first 90 days revealed similar results and therefore the data are not presented separately.

5.12.4. Multivariate analysis of patient mortality

5.12.4.1. Charlson index

The analysis showed that initial access had a significant impact on mortality as patients who started without permanent access had increased hazard of death of 2.4 times greater than those who started with AVF or graft. Each additional year of patient age increased their chance of death by 2%. Increases in Charlson score increased the risk of death by 1.9, 3.3 and 5.8 times in CCI 1, 2 and >2 respectively, compared with CCI of zero (**Table 5.37**). When the same analysis was done excluding those who died within the first 90 days, survival was affected by type of vascular access, CRP, referral 6 months previously, and comorbidity (**Table 5.38**).

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Age	0.038	1.02	1	1.04
Access	0.0001	2.42	1.47	3.96
CCI				
0	0.0001	Ref	-	
1		1.91	0.68	5.35
2		3.38	1.21	9.43
>2		5.8	2.27	14.81

Table 5.37; Cox regression survival analysis Charlson Index model

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Access	0.002	2.54	1.47	4.57
Referral at 6 months	0.017	2.07	1.14	3.75
CRP	0.029	1.01	1	1.02
CCI				
0	0.0001	Ref	-	
1		2.35	0.84	6.57
2		4.92	1.85	13.07
>2		8.6	3.63	20.79

Table 5.38; Cox regression survival analysis Charlson Index model excluding 90 days mortality

5.12.4.2. Khan score

This analysis showed that access and serum cholesterol are significant predictors of mortality. Each 1mmol/l increase in initial serum cholesterol decreased the hazard of death by 22%. Patients in the medium and high risk groups had increased risk of death by 6.4 and 13.6 times respectively, than low risk group (**Table 5.39**). The same analysis excluding 90 days mortality showed that patients who started haemodialysis with temporary access had risk of death by 3.3 times higher than those who started with AV fistula/ graft. Patients who had not been referred 6 months prior to their first haemodialysis session had 2.1 times higher risk of death than those who had been referred. The risk of death was increased by 6.2 and 14.2 times greater in medium and high risk Khan score groups compared with low risk group (**Table 5.40**).

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Access	0.0001	2.71	1.65	4.45
Cholesterol (mmol/l)	0.015	0.78	0.64	0.95
Khan				
Low risk group	0.0001	Ref	-	
Medium risk group		6.49	1.87	22.54
High risk group		13.83	4.31	44.38

Table 5.39; Cox regression survival analysis Khan score model.

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Access	0.0001	3.31	1.85	5.92
Referral 6 months	0.009	2.15	1.21	3.81
Khan				
Low risk group	0.0001	Ref	-	
Medium risk group		6.2	1.77	21.73
High risk group		14.28	4.39	46.43

Table 5.40; Cox regression survival analysis Khan score model excluding 90 days mortality

5.12.4.3. Davies score

The analysis using Davies score including and then excluding those who died within the first 90 days showed the same results as obtained when Charlson score was used **(Table 5.41 and 5.42)**., except that cholesterol was an independent risk factor for death when those who died within 90 days were included.

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Age	0.03	1.02	1.01	1.04
Access	0.0001	2.52	1.5	4.21
Cholesterol	0.033	0.79	0.64	0.98
Davies				
0	0.0001	Ref	-	
1		5.58	2.02	15.41
2		9.2	3.48	24.31
>2		11.67	4.54	30.02

Table 5.41; Cox regression survival analysis Davies score model

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Access	0.0001	2.68	1.46	4.89
Referral 6 months	0.008	2.31	1.25	4.27
CRP	0.047	1.01	1	1.02
Davies				
0	0.0001	Ref	-	
1		5	1.77	14.09
2		8.9	3.3	24.06
>2		11.93	4.55	31.25

Table 5.42; Cox regression survival analysis Davies score model excluding 90 days mortality

5.12.4.4. Comorbid conditions

All comorbid conditions that had been considered in this study had been entered in this model separately to find the comorbid illness that had the most significant impact on mortality. Congestive cardiac failure is the only comorbid condition that had a significant influence on mortality of haemodialysis patients. Those who started haemodialysis with congestive cardiac failure had increased risk of death by 2.2 times greater than who started without congestive cardiac failure **(Table 5.43)**.

Excluding those who died within the first 90 days of haemodialysis treatment the analysis showed that congestive cardiac failure and ischaemic heart disease were significant contributors to risk of mortality. Congestive cardiac failure and ischaemic heart disease increased the risk of death by 2.6 and 1.7 times respectively (**Table 5.44**).

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Age	0.0001	1.03	1.01	1.04
Access	0.0001	2.26	1.37	3.74
Cholesterol	0.015	0.78	0.63	0.95
Congestive cardiac failure	0.0001	2.24	1.4	3.57

Table 5.43; Cox regression survival analysis all comorbid conditions model

Variable	significance	Hazard ratio	95% CI for Hazard ratio	
			lower	upper
Age	0.002	1.03	1.01	1.05
Access	0.0001	2.34	1.48	3.96
CCF	0.0001	2.62	1.59	4.31
IHD	0.027	1.76	1.06	2.91

Table 5.44; Cox regression survival analysis all comorbid conditions model excluding 90 days mortality

5.12.5. Summary of survival analysis of haemodialysis patients

The mortality of incident haemodialysis patients was 30.1% at one year and 53.8% at end of the study which reduced to 23.8% and 49.7% when 90 days mortality was excluded. The most common cause of death was cardiovascular 41%, followed by infection 27.7%. Univariate analysis showed that age, comorbidity, initial access, initial serum albumin, cholesterol and CRP were all associated with mortality at the end of the study. Multivariate analysis revealed that when all factors were entered together age, comorbidity, starting dialysis with permanent access, and initial serum cholesterol were significantly associated with death at the end of the study. When all comorbid conditions were entered as independent factors, congestive cardiac failure

is the only comorbid illness that was associated significantly with mortality in haemodialysis patients. Ischaemic heart disease was a significant risk factor for mortality of haemodialysis patient when 90 days mortality was excluded. Gender, whether or not patients were referred early, and primary renal diagnosis did not contribute significantly to the survival analysis.

Chapter 6

Survival comparison between 2001 and 2006 Studies

6.1. Abstract

Introduction

Edinburgh showed 1 year survival below the 95th centile in the Renal Registry 2006 analysis of patients commencing dialysis in 2004. However, long term survival figures are not significantly different from other units in Scotland.

Aim

To examine factors associated with survival in a detailed analysis of the cohort commencing dialysis in south east Scotland in 2003 and 2004 and compare with a prior cohort commencing dialysis from 1997 until 2000. These cohorts initiated RRT before and after moving to a new hospital.

Method

183 patients started RRT in South East Scotland in 2003-2004, 156 haemodialysis, 25 peritoneal dialysis and 2 as pre-emptive transplants. Comorbidity was scored according to the age and number of comorbid condition and patients stratified into 3 risk groups. Univariate and multivariate Cox regression was used to identify the independent predictors of survival. The main outcomes were overall survival and hospitalisation.

Results

Between the two studies the median age rose from 63 to 65 and take on rate from 83 to 91.5 patients per year (approximately from 113 to 120 patients per million population per year) with all of the increase being in the Khan high risk group. Mortality of the recent cohort was 7% at 90 days, 26% after at one year and 38% at two years. In the previous cohort these figures are 9%, 21% and 37% respectively. Multivariate analysis revealed that comorbidity group, permanent access, initial serum albumin and initial serum cholesterol were independent predictors of mortality. The median percentage of hospitalisation was halved in the recent study.

Conclusion

The 2 years survival rate was essentially unchanged between both studies despite accepting older and more "high risk" patients in the recent study. Severity of comorbidity is an important predictor of survival.

6.2. Introduction

Survival is the ultimate outcome that can be used to compare the services between different renal units. This chapter presents information about the outcomes being achieved in the Royal Infirmary of Edinburgh Renal Unit in comparison with other UK renal units according to UKRR report 2006 and with Scotland renal units according to Scottish Renal Registry (SRR) reports 2002-2004. An incident cohort study, which included 183 patients who started RTT in 2003 and 2004, was designed to investigate about the survival changes (improvement, deterioration or no change) in dialysis patients in the RIE renal unit in comparison with data has obtained from a study conducted in 2001 in the RIE renal unit that included 249 incident patients who started RTT between 1997 and 2000. In addition, to find the possible factors that could be associated with patients' survival were determined.

The SRR report 2002-2004 includes data from all the Scottish Renal Units and showed the survival of patients receiving RRT over a 10 year period. The Crosshouse renal unit (XH) was used as a reference with a median survival time of 3.8 years. The graph shows very little difference in survival between all adult renal units; the only exception was the Royal Hospital for Sick Children Glasgow (RHSC) (paediatric renal unit) which had the best survival as expected. The risk of death at RIE was 1.06 (95% CI 0.88 – 1.27) times greater than the reference unit (XH) **(Figure 6.1)**.

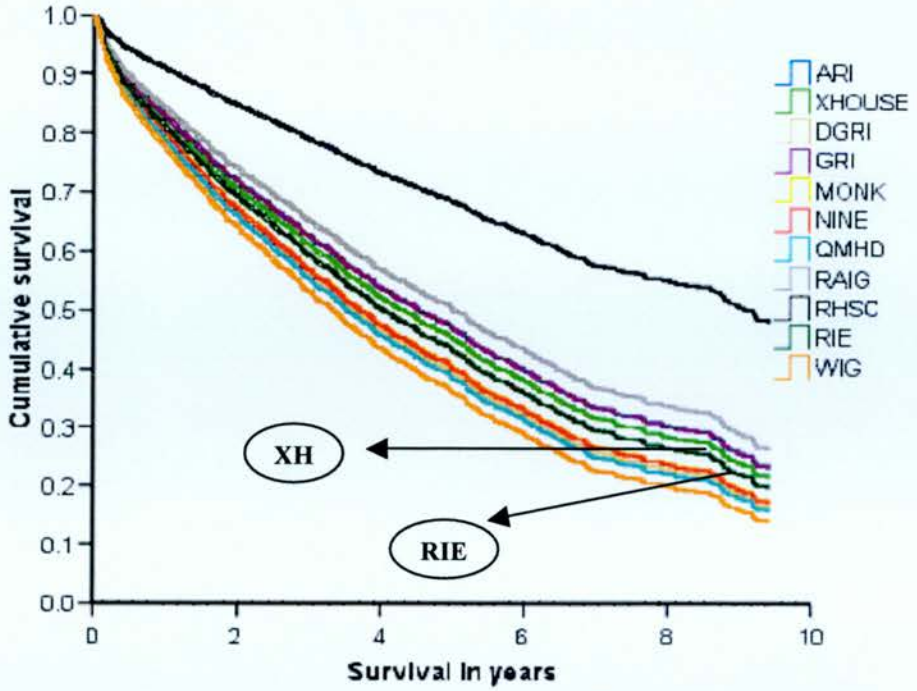

Figure 6.1; Survival by renal unit providing first RRT between 1995 and 2004
Courtesy of Scottish Renal Registry 2004

However, the funnel plot **(Figure 6.2)** presented in the UKRR annual report (2006) shows one year survival of all renal units in UK with the mean survival of 87% and dotted lines denoting 99% CI and 95% CI from the mean. The lowest survival in all UK units was recorded in Plymouth (78.7%). Of all Scotland renal units the highest was 88.3% in Aberdeen Royal Infirmary (ARI) and lowest was 81% in Dumfries and Galloway (DGRI). The mean survival of Edinburgh renal unit was 82% just below the 95% CI. This survival percentage gave Edinburgh the 4th lowest survival of all UK renal units, but it was fairly typical of southern Scotland. However, the case was different in 2007 UKRR report as the mean survival of Edinburgh renal unit rose to 86% but the survival of incident dialysis patients in Scotland was significantly lower than in the rest of the UK.

Although Edinburgh's very low position seems likely to be a chance event on a background of relatively poorer survival for all Scottish units; it was important to examine this more closely

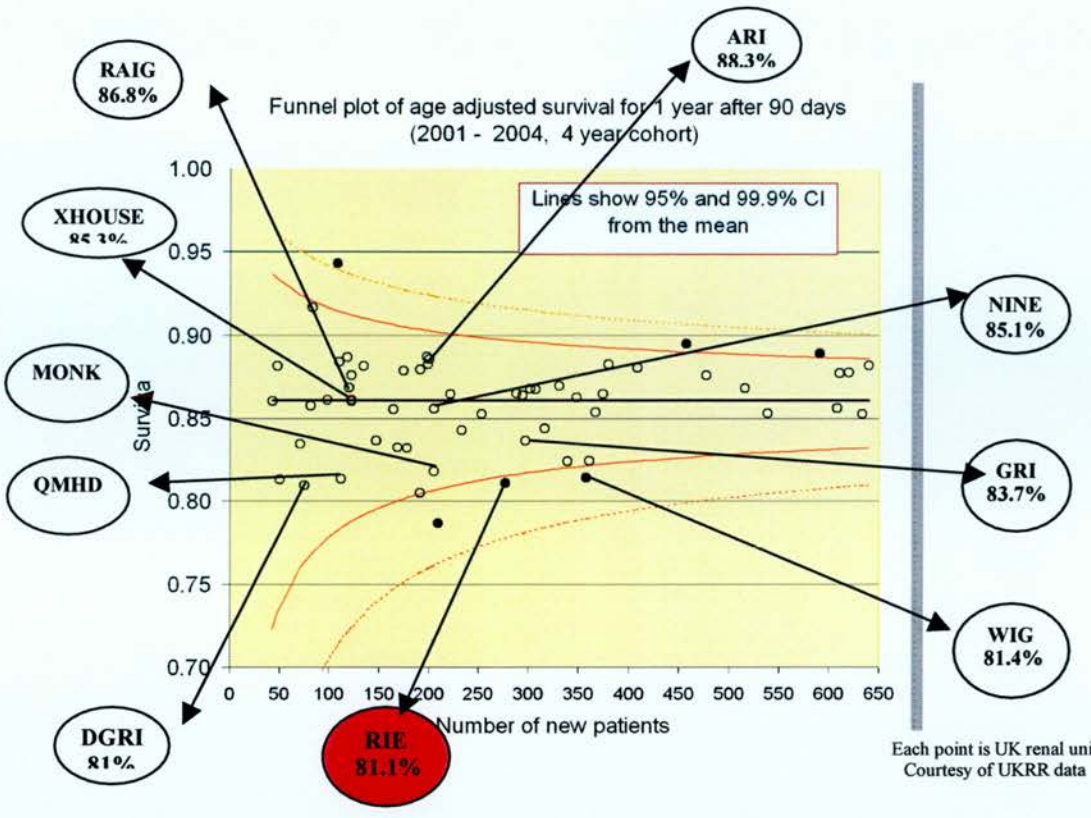

Figure 6.2: Funnel plot of age-adjusted survival for 1 year after 90 days (2001 – 2004, 4 year cohort) each point is UK renal unit. From the UKRR report 2004.
Courtesy of Scottish Renal Registry 2004

Fortunately a study conducted in 2001 which included 249 incident adult patients who started RRT between July 1997 and June 2000 (a cohort before the UKRR report) was available to give us the opportunity to compare it with the survival of patients who initiated dialysis in 2003 and 2004. This cohort was followed until 2006 hence this will be referred to as the 2006 cohort. The 2006 study involved a cohort that was included in the 2006 UKRR report

The 2001 study included all adult patients who started RRT over a 3 year period between 1997 and 2000. Mortality was related to comorbidity and age using a modified Khan score (it is the same as the Khan score but with less comorbid conditions congestive cardiac failure, chronic pulmonary disease and liver disease). 249 patients were classified into 3 groups according to Khan score. The number of patients in each risk group with median age and survival percentage at 90 days, 1 year and 2 years are shown in **Table 6.1.** The study showed that overall two years

survival was 63% and the outcomes were excellent for low and medium risk group but the mortality of the high risk group was high, thought not different from comparable studies (Edren).

Risk group	number	Median age	Survival		
			90 days	1 year	2 years
Low risk	90 (36.1%)	49 (17 - 69)	99	96	93
Medium	84 (33.7%)	71 (34 – 87)	92	76	63
High	75 (30.1%)	67 (34 – 87)	81	63	33
Overall	249	63 (17 – 87)	91	79	63

Table 6.1; Survival of RRT in Edinburgh (2001)

6.3. Methods

In this study, the data presented in chapter 5 is reanalysed in the same way of the previous study in 2001 to permit direct comparisons. Unlike chapter 5 the follow up period was exactly 2 years (minimum 7 days and maximum 730 days) or until death. In the 2001 study only five comorbid diseases were collected **(Table 6.2)**. Patients were assigned to risk groups based on age and the number of comorbidities (explained in the above section) **Table 6.3**

Comorbid diseases
1. Ischemic Heart Disease (Angina, Myocardial infarction, PTCA/CABG)
2. Cerebrovascular (TIA, CVA)
3. Peripheral vascular disease (intermittent claudication, amputation, PV bypass)
4. Diabetes
5. Visceral malignancy (not including skin cancer)

Table 6.2; Comorbid diseases included in 2001 study

Risk groups	
Low risk	Age <70 years
Moderate risk	Age 70-79 years Age <70 years with one comorbidity out of 1,2,3,4
High risk	Age ≥80 years Any age with two comorbidities out of 1,2,3,4 Any age with visceral malignancy

Table 6.3; Classification of comorbidity risk groups

6.4. Frequency and distribution of patients in 2001 and 2006 studies

6.4.1. Age and Gender

The total number of patients involved in 2001 was 249 collected over 3 years whereas in 2006 183 patients were collected in 2 years. Between two studies the median age rose from 63 to 65 and take on rate from 83 to 91.5 patients per year (approximately from 113 to 120 patients per million populations per year) **Table 6.4.** The proportion of patients above 75 years was higher in 2006 (25.7%) compared with 19.2% in the 2001 study. The gender proportions in both studies were almost the same. The number of male patients was higher than female patients **(Table 6.4)**. The significance (P value) between age groups of both studies was not tested because we lacked the detailed information of patients involved in 2001 study.

	2001	2006
Age group		
15-49	57 (22.8)	44 (24)
50-64	79 (31.8)	42 (23)
65-74	65 (26.2)	50 (27.3)
≥75	48 (19.2)	47 (25.7)
Gender		
Male	143 (57)	100 (54.6)
Female	106 (43)	83 (45.4)
Total	**249**	**183**

Table 6.4; Number and percentage of age group and gender in 2001 and 2006 studies

6.4.2. Modality

Haemodialysis was the dominant modality of treatment, 75.9% in 2001 and 85.2% in 2006 with the highest median age 64 years and 67 years respectively, followed by

peritoneal dialysis, and pre-emptive transplant (**Table 6.5**). Chi square tests showed a significant association between age group and mode of first RRT 2001 (p=0.014), and in 2006 (p=0.05).

Modality	**2001**		**2006**	
	Number	Median age (IQR)	Number	Median age (IQR)
Haemodialysis	189 (75.9%)	64 (22 – 87)	156 (85.2)	67 (54 – 76)
Peritoneal dialysis	56 (22.5%)	58 (17 – 80)	25 (13.7%)	53 (42.5 – 67)
Transplant	4 (1.6%)	38.5 (17 – 55)	2 (1.1%)	37 and 59

Table 6.5; Number, percentage and median age of patients in 2001 and 2006 according to modality of treatment

6.4.3 Referral

Referred and not-referred to nephrology care was defined using the time from the date of first biochemical test to the date of first RRT treatment. Patients were classified as not-referred if this time was under 90 days. The proportion of referred and not-referred patients was almost equal in the 2 studies (**Table 6.6**).

	2001	**2006**
Referred	185 (74%)	134 (73%)
Not-referred	64 (26%)	49 (27%)

Table 6.6; the number and proportion of treatment type in 2001 and 2006 studies

Chi square tests showed a significant association (p=0.002) in 2001 and (p=0.005) in 2006 between referred/ not-referred and mode of first RRT with 70.2% and 80.6% of all referred cases starting RRT on haemodialysis in 2001 and 2006 respectively (**Table 6.7**).

Modality	2001		2006	
	Referred	Not-referred	Referred	Not-referred
Haemodialysis	130 (70.2)	59 (92.2)	108 (80.6)	48 (97.9)
Peritoneal dialysis	51 (27.6)	5 (7.8)	24 (17.9)	1 (2.1)
Transplant	4 (2.2)	0	2 (1.5)	0
Total	**185**	**64**	**134**	**49**

Table 6.7; First modality of RRT in relation to referral in 2001 and 2006 studies

There was no significant association between referred or not-referred treatment and age group (Chi-Square test, p=0.654 for 2001, and p=0.107 for 2006) **(Table 6.8).**

Age group	2001		2006	
	referred	Not-referred	Referred	Not-referred
15-49	44 (23.8)	13 (20.3)	35 (26.1)	9 (18.4)
50-64	56 (30.3)	23 (35.9)	35 (26.1)	7 (14.3)
65-74	51 (27.6)	14 (21.8)	31 (23.2)	19 (38.8)
≥75	34 (18.3)	14 (21.8)	33 (24.6)	14 (28.5)
Total	**185**	**64**	**134**	**49**

Table 6.8; Age group in relation to referral in 2001 and 2006 studies

6.4.4. Primary Renal Disease

According to ERA-EDTA diagnosis codes for primary renal disease the new patients were classified into 8 groups in 2001 study **(Table 6.9)** and 5 groups in 2006 study **(Table 6.10)**. The proportion of patients who started dialysis with diabetes were 20% in the 2001 study and 24% in the 2006 study but only 14% and 19% were diagnosed with diabetic nephropathy respectively.

Primary renal diagnosis	no	%	Median age
Primary glomerulonephritis	39	16	57
Interstitial nephritis	36	14.2	53
Familial /Hereditary. Renal diseases	29	12	53
Congenital diseases	2	0.8	24.5
Vascular diseases	54	21.6	71.5
Secondary glomerulonephritis/ systemic disease	47	18.6	63
Miscellaneous	8	3.2	62
Unknown	34	13.6	70.5

Table 6.9; Distribution and median age of new patients by primary renal disease in 2001 study

Primary Renal Diagnosis	No	%	Median age (IQR)
Glomerulonephritis	41	22.4%	62 (41-71)
Interstitial Nephritis	34	18.6%	59 (42-70)
Multisystem Disease	52	28.4%	67 (56-79)
Diabetic Nephropathy	19	10.4%	61 (45-68)
Not known and Others	37	20.2%	74 (65-80)

Table 6.10; Distribution and median age of new patients by primary renal disease in 2006 study

6.5. Comparison of the Survival analysis between 2001 and 2006 studies

The extra patients commencing dialysis in the later study fall almost entirely in the high risk group which has a higher median age than the earlier study. **(Table 6.11)**

Risk group	No of cases & %		Median age (min & max)	
	2001	2006	2001	2006
Low	90 (36)	56 (31)	49 (17 – 69)	42 (18 – 68)
Medium	84 (34)	52 (28)	71 (34 – 87)	69 (31 – 84)
High	75 (30)	75 (41)	67 (34 – 87)	73 (39 – 88)
Total	**249**	**183**	**63 (17 – 87)**	**65 (18 – 88)**

Table 6.11; Comparison of the patient number and median age according to risk groups between 2001 and 2006 studies

Table 6.12 shows the outcome in the two studies:-

1. At 90 days the percentage of overall survival was slightly higher in 2006 than 2001 (93% vs. 91%) and according to risk groups the low and high risk groups survival were slightly higher in 2006 than 2001.
2. At 1 year the overall survival was higher in 2001 than 2006 (79% vs. 74%),
3. The percentage of overall survival at 2 years was unchanged in both studies (63% vs. 62%).
    - The survival of low risk group in 2001 was higher than 2006 but most importantly this apparent 7% survival difference was made by 1 dead patient (the number of dead patients in 2001 was 7 out of 90 whereas in 2006 was 8 out of 56).
    - The medium risk group survival was almost the same in both studies.
    - Although in 2006 study the total number of patients was lower than 2001, the same number of high risk group patients was recorded in both studies (75 patients), making the proportion of high risk patients in 2006 higher than in 2001. However the survival of high risk group in the 2006 study was better than in the 2001 study (44% vs. 33%).The significant difference between risk groups of both studies was not tested because we lack the detailed information of patients included in 2001 study.

Risk group	90 days				1 year				2 years			
	2001		2006		2001		2006		2001		2006	
	%	no	%	no	%	no	%	no	%	no	%	no
Low	99	89	100	65	96	86	91	51	93	83	86	48
Medium	92	77	91	47	76	63	75	39	63	52	62	32
High	81	65	89	67	63	47	60	45	33	24	44	33
Total	**91**	**231**	**93**	**170**	**79**	**196**	**74**	**135**	**63**	**159**	**62**	**113**

Table 6.12; Comparison of survival percentage according to risk groups between 2001and 2006

6.6. Comparison of hospitalisation between 2001 and 2006 studies

The median percentage of live time spent in hospital in 2006 study (time from starting RRT to either death or exact 2 years) was calculated for each patient. Kruskal Wallis test was used to compare the hospital data of 2001 (**Table 6.13**) with 2006 (**Table 6.14**) according to age group and risk groups (p value <0.05 was significant).

The overall median percentage of time at risk spent in hospital in 2001 was 2 times higher than in 2006 (8% vs. 4.1%). Hospitalisation was lower for all risk groups in the recent study. The results showed that for both studies the percentage of time at risk spent in hospital was highest for patients aged ≥75 (10.1% for 2001, and 11% for 2006). The percentage of time spent in hospital was increased markedly by risk group (12% of time for high risk vs. 3.9% for low in 2001, and 10% for high risk vs. 2.2% for low in 2006). There were significant differences in percentage of time at risk spent in hospital between age groups and risk groups.

	patients	Median	IQR	Kruskal-Wallis test (p-value)
Age Group				0.002
15 – 49	57	3.4	1.4 – 7.6	
50 – 64	79	7.4	3.2 – 18.6	
65 – 74	65	8.5	3.3 – 23.4	
≥75	48	10.1	3.6 – 18.2	
Risk Group				0.0001
Low	90	3.9	1.4 – 7.4	
Medium	84	8.3	3.6 – 14.7	
High	75	12	3.5 – 27.8	

Table 6.13; Percentage of time at risk spent in hospital in 2001 study

	patients	Median	IQR	Kruskal-Wallis test (p-value)
Age Group				0.0001
15 – 49	44	1.8	0.6 – 4	
50 – 64	42	3.8	1.2 – 10.8	
65 – 74	50	6.5	1.8 – 20.7	
≥75	47	11	1.5 – 25.9	
Risk Group				0.0001
Low	56	2.2	0.6 – 4.4	
Medium	52	4.6	1.5 – 13.2	
High	75	10	1.9 – 23	

Table 6.14; Percentage of time at risk spent in hospital in 2006 study

6.7. Survival analysis of 2006 study at 2 years

The survival analysis in this chapter is different from chapter 5 regarding the period of follow up as already explained in chapter 2. The survival results will show the factors that associated with patients survival when the period of follow up is equal for all patients (730 days) unless the patient died.

6.7.1. Univariate analysis

Univariate analysis including patients who died within the first 90 days, showed that age, comorbidity based on modified khan score that used in the 2001 study, initial access for RRT, initial mode of RRT, initial serum albumin, initial serum cholesterol, and initial CRP were all significantly associated with death within two year of starting dialysis (**Table 6.15).** The same univariate analysis was repeated excluding those patients who died within the first 90 days revealed that the same factors listed above were significantly associated with patient mortality (**Table 6.16).**

Univariate analysis of all coexisting illnesses at start of RRT revealed that congestive cardiac failure, ischemic heart disease, chronic pulmonary disease and malignancy were significantly associated with death in both analyses that included and excluded patients who died in the first 90 days of starting RRT. Patients' sex did not influence survival, nor did primary renal diagnosis, haemoglobin concentration, eGFR, or urea concentration at time of initiating RRT.

	Cohort n=183	2 year survivors n=113	Dead by 2year n=70	p value & statistic test
Median age (years) (IQR)	65 (50-75)	59 (42-71)	71 (64-78)	p=0.0001 M-W
Age≥65 years	97 (53)	48 (42.9)	63 (69)	p=0.0001 χ^2
Referral 3 m	132 (72.9)	86 (78.2)	46 (64.8)	p=0.048 χ^2
Referred 6 m	125 (69.1)	81 (73.6)	44 (62)	p=0.097 χ^2
Access (HD+PD)	89 (49.2)	72 (65.5)	17 (23.9)	p=0.0001 χ^2
Access haemodialysis	64 (41)	50 (56.8)	14 (20.6)	p=0.0001 χ^2
First Mode of RRT				p=0.003 χ^2
Haemodialysis	156 (86.2)	88 (80)	84 (95.8)	
Peritoneal dialysis	25 (13.8)	22 (20)	3 (4.2)	
Primary renal diagnosis				p=0.131 χ^2
Glomerulonephritis	41 (22.4)	28 (25)	13 (18.3)	
Interstitial Nephritis	34 (18.6)	25 (22.3)	9 (12.7)	
Multisystem disease	52 (28.4)	28 (25)	24 (33.8)	
Diabetic nephropathy	19 (10.4)	13 (11.6)	6 (8.5)	
Unknown	37 (20.2)	18 (16.1)	19 (26.8)	
Mean Albumin (g/l)	33.6	35.3	30.9	p=0.0001 T-test
Mean cholesterol (mmol/l)	4.5	4.6	4.1	p=0.003 T-test
Median CRP (mg/l) (IQR)	15 (5-49)	7 (4-22)	34 (15-97)	p= 0.0001 M-W
Comorbid Conditions				
Congestive cardiac failure	70 (38.3)	24 (21.4)	46 (64.8)	p=0.001 χ^2
Ischaemic heart disease	62 (33.9)	28 (25)	34 (47.9)	p=0.0001 χ^2
Malignancy	19 (10.4)	6 (5.4)	13 (18.3)	p=0.005 χ^2
Chronic pulmonary disease	24 (13.1)	7 (6.3)	17 (23.9)	p=0.001 χ^2
Connective tissue disease	16 (8.7)	5 (4.5)	11 (15.5)	p=0.021 χ^2
Comorbidity				p=0.0001 χ^2
Low	56 (30.6)	48 (42.5)	8 (11.4)	
Medium	52 (28.4)	32 (28.3)	20 (28.6)	
High	75 (41)	33 (29.2)	42 (60)	

Table 6.15: Patient characteristics and univariate analysis at two years, M-W=Mann-Whitney Test, χ^2 = Chi square, IQR= inter-quartile range,

	Cohort n=170	2 year survivors n=113	Dead by 2year n=57	p value & statistic test
Median age (years) (IQR)	65 (48-74)	59 (42-71)	70 (62-77)	p=0.0001 M-W
Age≥65 years	88 (51.8)	48 (42.9)	40 (69)	p=0.001 χ^2
Access (HD+PD)	89 (53)	72 (65.5)	17 (29.3)	p=0.0001 χ^2
Access Haemodialysis	64 (44.8)	50 (56.8)	14 (25.5)	p=0.0001 χ^2
First Mode of RRT				p=0.010 χ^2
Haemodialysis	143 (85.1)	88 (80)	55 (94.8)	
Peritoneal dialysis	25 (14.9)	22 (20)	3 (5.2)	
Mean Albumin (mg/l)	33.8	35.3	31.7	p=0.0001 T-test
Mean cholesterol (mmol/l)	4.5	4.6	4.2	p=0.003 T-test
Median CRP (mg/l) (IQR)	13 (5-47)	8 (4-22)	34 (14-91)	p= 0.0001 M-W
Comorbid Conditions				
Congestive cardiac failure	59 (34.7)	24 (21.4)	35 (60.3)	p=0.0001 χ^2
Ischaemic heart disease	55 (32.4)	28 (25)	27 (46.6)	p=0.004 χ^2
Chronic pulmonary disease	22 (13.1)	7 (6.3)	15 (25.9)	p=0.0001 χ^2
Malignancy	17 (10)	6 (5.4)	11 (19)	p=0.005 χ^2
Comorbidity				p=0.0001 χ^2
Low	56 (32.9)	48 (42.5)	8 (14.1)	
Medium	47 (27.6)	32 (28.3)	15 (26.3)	
High	67 (39.4)	33 (29.2)	34 (59.6)	

Table 6.16: Patient characteristics and univariate analysis at two years excluding 90 days deaths M-W=Mann-Whitney Test, χ^2 = Chi square, IQR= inter-quartile range,

6.7.2. Multivariate analysis of 2006 study

The independent variables used in the multivariate analysis were gender, first modality of treatment, referral to nephrology care, definitive access, serum-, albumin, urea, cholesterol, and CRP, primary renal diagnosis (based on ERA-EDTA codes for renal disease), and comorbidity effect that evaluated by the same score that has been used by 2001 study which stratifies patients into 3 risk groups (mild, medium and high) depending on age and that is why age was not included in the analysis. The main outcome was 2 years patient survival with binary description (1= death, 0 = live). Gender, modality, treatment type were also a binary variables.

The analysis revealed that initial access for RRT was significantly (p=0.0001) associated with survival as patients who started dialysis with no access have an increased risk of death by 3.5 times greater than those who started dialysis with permanent access including both haemodialysis and peritoneal dialysis patients. Higher initial serum cholesterol had a beneficial effect upon survival; each 1mmol/l increase in serum cholesterol decreased the hazard of death by 28%. Each 1g/l increase in serum albumin decreased the hazard of death by 4%. Comorbidity risk was significantly increased the risk of death by 2.6 times and 3.6 times in the medium and high risk groups respectively, compared with the reference low risk group (**Table 6.17**).

Variable	**significance**	**Hazard ratio**	**95% CI for Hazard ratio**	
			lower	upper
Access	0.0001	3.5	1.93	6.52
Cholesterol	0.004	0.72	0.58	0.90
Albumin	0.049	0.96	0.92	0.98
Comorbidity	0.0001	Ref		
Moderate risk group		2.61	1.16	6.22
Severe risk group		3.62	1.65	7.88

Table 6.17; Cox regression survival analysis of 2006 study

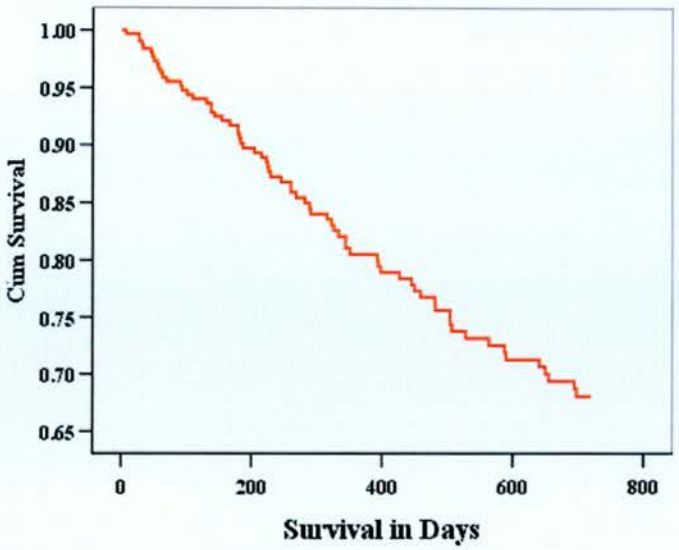

Figure 6.3: Two year Survival curve of incident patients started RRT in RIE in 2003 and 2004.

6.8. Summary

Two years survival rate was essentially unchanged between both studies despite accepting older and more "high risk" patients in the recent study. Severity of comorbidity was an important predictor of survival. It is not apparent from this data why Edinburgh along with most of the rest of Scotland, has poorer survival on RRT. However the poorer survival of the background population seems likely to be relevant. A reduction in hospitalisation was noted occurred across a period of moving to a new hospital and multiple changes in working practices and in patient supervision and audit policies.

Chapter 7

Discussion, Conclusions and Recommendations

Discussion

7.1. Introduction

Figure 7.1 illustrates the summary of univariate and multivariate results in chapters 4, 5 and 6. According to these results I will discuss individually the multivariate independent factors that associated with patient survival, supported by the univariate results. However before that a summary and limitations assessments of each chapter are discussed.

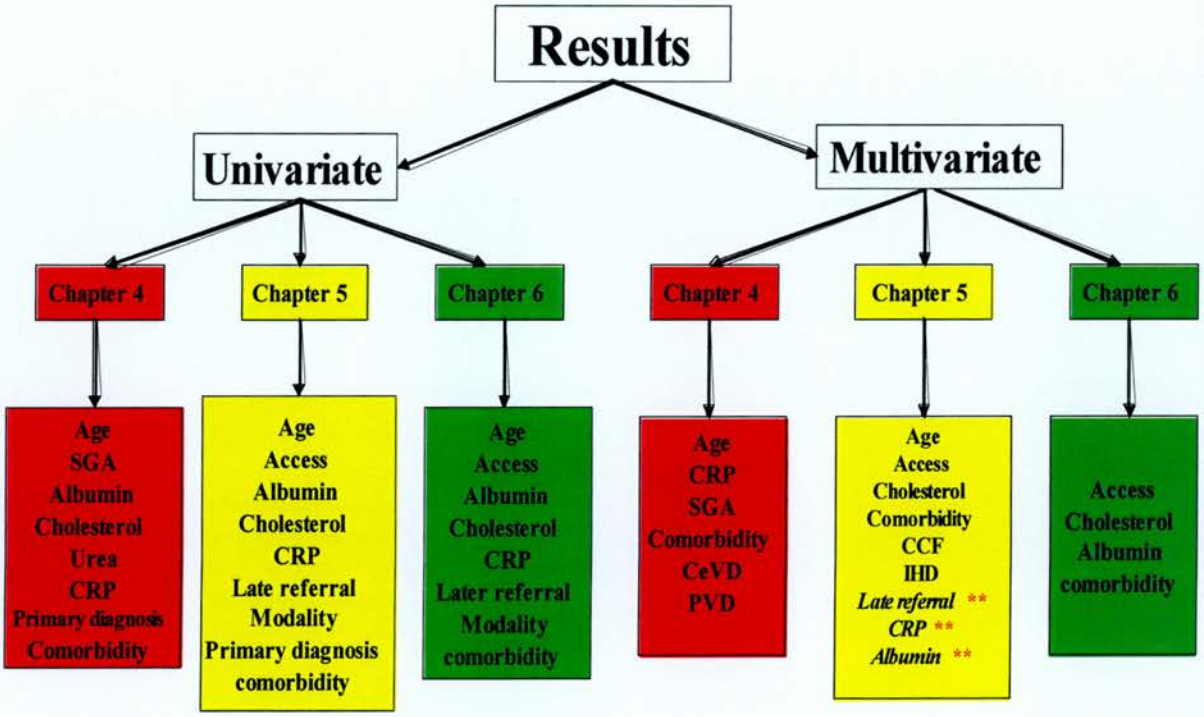

Figure 7.1; Summary of univariate and multivariate analysis in c hapters 4, 5 and 6
** late referral - when patients who died within the first 90 days excluded
** CRP - when haemodialysis patients only included
** Albumin - when all comorbid conditions were enter in analysis instead of u sing single comorbid score

7.2. Summary and limitations of chapters 4, 5 and 6

7.2.1. Chapter 4

Despite this study having a cross sectional design, its results are like other survival studies in that patient survival was influenced by age and burden of comorbid illnesses, in addition to SGA and CRP. Presence of cerebrovascular disease and peripheral vascular disease at the start of the study were the only contributory illnesses to patient mortality. Hospitalisation percentage was markedly increased by older age, high risk group, and malnourishment.

This study should be qualified by the possibility of selection bias during the initial recruitment, it is possible that only those dialysis patients who were generally healthier agreed to participate. However, the results of our study showed the one year survival of our sample (122 patients) was similar to the one year overall survival of all prevalent patients (298 patients) at the same hospital in the same year (87.7% vs. 87.4%).

The dietician team who initiated this study were aiming to find a nutritional screening tool that was less time consuming, with the suggestion that a computer based malnutrition screening tool could identify dialysis patients at risk of malnutrition as accurately as subjective global assessment (SGA). However, survival analysis of this study revealed that only SGA predicted survival out of other numerical and measurable nutritional markers.

7.2.2. Chapter 5

This study addressed the factors that have negatively influenced survival and increased hospital admission of patients starting RRT in Edinburgh in 2003 and 2004. Survival was affected by increased age, presence of comorbid conditions, starting treatment with temporary access, and level of serum cholesterol. Out of all comorbid conditions that were collected at the start of patient treatment, congestive cardiac failure and ischaemic heart disease were the most important diseases that affected patient survival. Hospitalisation was higher in old age, high risk patients, females and those who started dialysis with temporary access

The limitations of this study were; - the number of involved patients was small. The proportion of peritoneal dialysis was also small which did not allow us to compare between the two dialysis modalities.

The other limitation in this study is using Kaplan Meier method in comparing patient survival on haemodialysis and peritoneal dialysis. There were very few patients receiving peritoneal dialysis and therefore the results of the Kaplan-Meier analysis in this context must be viewed with caution

A further potential limitation of the study is the possibility of lead time bias. This kind of limitation may lead to differences between countries and renal centers in measuring survival from the start of RRT. For example, apparent survival will be longer if RRT is started at GFR=10 than in those who started with at GFR=5 as it is measured from a time point earlier in the course of the disease. However, lead time bias is unlikely a factor in this study because it is a single center study.

7.2.3. Chapter 6

The controversy created by the UKRR report on short term survival and SRR report on long term survival of Edinburgh renal patients was unit investigated by comparing the outcomes of patients started dialysis in 2003 and 2004 with the outcomes of a previously conducted study in 2001 in the same renal unit. The comparison revealed that overall survival was unchanged between both studies despite accepting older and more high risk patients in 2006 study and there was a substantial reduction in hospitalisation in 2006 study. Severity of comorbidity, serum albumin, serum cholesterol and starting dialysis with permanent access were important predictors of survival in patients started dialysis in 2003 and 2004.

There were several changes in practice between the two studies: the unit moved hospitals and gained more nephrologists, more machines, there was a greater use of high flux dialyzers and more rigorous audit was implemented particularly in the haemodialysis services. However, we do not know for certain if these changes could

explain the improvement in survival of high risk patients especially when we consider the disappointing results from the HEMO study of no significant survival advantages from using high rather than low flux dialyzers.

The limitation includes small number of patients with inadequate statistical power to compare the high risk group in both studies.

7.3. Factors associated with survival

7.3.1. Age

The median age of the incident patients in Edinburgh has risen from 63 years (range 17- 87) in 2001 to 65 years (range 18-88) in 2006. Similarly, the median age of incident dialysis patients in Scotland and the UK, has been increased from 63.9 and 63 years in 1998 to 65.5 and 65 years in 2007 respectively (Ansell et al., 2007).

The number of elderly patients requiring RRT has increased worldwide. In 1980, USRDS reported that 28.5% of dialysis patients were ≥ 65 years of age. In 2000, the same age group had increased to 49.9% (USRDS 2007). The UKRR showed that the percentage of new patients who are over 65 years of age has increased from 43% in 1987 to 51.2% in 2006 (Ansell et al., 2007). In Edinburgh 52.7% of patients who started dialysis in 2003 and 2004 were ≥ 65 years.

Age is the most powerful factor associated with survival in patients receiving RRT. Multivariate analysis in chapter 4 and 5 showed that each additional year of patient age increased the risk of death by 5% in prevalent patients and 3% in incident patients. The UKRR (2005) reported that for every 10 year increase in patient age, there is an increase in the hazard of death of 41% (Ansell et al., 2005).

The mortality rates of patients starting dialysis in 2003 and 2004 in Edinburgh were 7.7% at one year and 12% at two years in young patients (<65 years) compared with 18.6% at one year and 26.2% at two in old patients (≥ 65 years), However these figures are much lower than reported from UK and US especially for old patients. In 2007, the UKRR reported the difference in mortality rates of new dialysis patients

according to same age groups were 10% at one year and 16% at two years in young patients whereas in old patients were 27% at one year and 45% at two years (Ansell et al., 2007). In the 2007 USRDS report when patients who were dead in the first 90 days excluded, the mortality rates in younger patients were 10% at 1 year, and 18% at two years but the mortality rates in patients ≥ 65 years were 30% at one year and 48% at two years (USRDS 2007).

7.3.2. Comorbidity

Comorbid disease is well recognized as an important determinant of clinical outcome, in terms of morbidity and mortality, for patients receiving RRT (Collins et al., 1990; and Khan et al., 1998). Comorbid conditions were very common in Edinburgh incident patients, 76% have one or more comorbid conditions. Congestive cardiac failure and ischaemic heart disease were the most common conditions, seen in 38% and 34% of patients respectively. The increased frequency of comorbidity was reported by UKRR (2007) where 55% of all patients starting RRT between 2001 and 2006 in centres reporting to the UKRR have one or more comorbidities. The most frequent comorbid diseases were diabetes 29% followed by ischaemic heart disease 24% (Ansell et al., 2007).

Analyses of our study demonstrated that comorbidity was associated with increased mortality at early (90 days), at one year and late at 2 years of follow up in dialysis patients starting RRT in Edinburgh. Similar observation of comorbidity associated with early mortality (90 days) has been publicized in a prospective study of 532 patients commencing RRT for ESRD in Scotland over one year, when comorbidity was assessed using Khan score to classify patients into 3 risk groups. They found that comorbidity was associated with early mortality (first 90 days) and patients in medium and high comorbidity risk groups had early mortality rates of 2.2 and 4.7 times greater than those in the low-risk group (Metcalfe et al., 2000). Also similar observations of comorbidity association with late mortality (2 years) were shown in an observational study of 523 patients starting RRT in Scotland over a 1 year period, followed for the first 2 years when Charlson index was used to group patients according to comorbid conditions. They found increased comorbidity was a strong

predictor of poor outcome. Patients who scored more than 2 on the Charlson scale had 2.6 times the odds of death higher than those who started RRT with no comorbid condition over 2 years (Metcalfe et al., 2003). The DOPPS study showed that different comorbid conditions were associated with increased mortality among haemodialysis patients (Goodkin et al., 2003).

The above observations of poorer outcomes influenced by presence of comorbid disease at start of RRT is consistent with the UKRR (2006) that showed mortality within 90 days of starting RRT was influenced by presence of ischaemic heart disease, peripheral vascular disease, liver disease and malignancy. One year mortality was associated with ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, liver disease and malignancy (Ansell et al., 2006)

In chapter 5 comorbid conditions were assessed using three different comorbidity scores (Charlson, Khan, and Davies). The 3 comorbidity scores performed equally in predicting mortality, in agreement with van Manen and colleagues (2003). Therefore, Charlson, Khan and Davies scores may all be used to predict patient survival.

7.3.3. Late Referral

The percentage of incident patients who started RRT in 2003 and 2004 that was referred late (less than 90 days) was 28%. In developing countries, the proportion of patients referred late for nephrology care is as high as 62% (Sesso et al., 1996) while in developed countries it is ranges between 25% and 40% (Arora et al., 1999; Schmidt et al., 1998; and Roubicek e al. 2000)). In 2007, UKRR reported that the incidence of late referral (less than 90 days) ranged from 10 to 38% (Ansell et al., 2007).

Late referral may be a reflection of suboptimal pre-ESRD care as many observational studies showed that late referral associated with the following unfavourable consequences (Ratcliffe et al. 1984; Jungers et al., 1993; Eadington et al., 1994; Schmidt et al., 1998; and Roubicek et al., 2000): -

1. Poor control of blood pressure

2. Lower eGFR
3. Anaemia and lower haemoglobin concentration
4. Renal bone disease with low concentration of calcium and phosphate
5. Poor nutritional status as measured with serum albumin and BMI
6. Metabolic acidosis
7. Emergency haemodialysis
8. Increase frequency of temporary access use
9. Increase rate of hospitalisation and health care cost
10. Reduced chance of receiving kidney transplantation
11. Lack of psychological preparation for RRT

The univariate analysis in chapters 5 and 6 and multivariate analysis in chapter 5 revealed that late referral was associated with increased mortality in patients starting dialysis in 2003 and 2004. The increased mortality associated with late referral has been reported in several observational studies. In a study of 3104 dialysis patients showed that patients who referred late (<90 days) had 36% higher mortality rate compared with those who had early referred to nephrology care. Excess mortality among late referral was limited to the first 3 months of dialysis but not present thereafter (Winkelmayer et al., 2003). A study which evaluated the impact of early nephrology referral and pre-ESRD care on mortality risk in 2246 new dialysis patients from USRDS found the mortality risks were higher for late referral (<4 months) compared with early referral patients (1.68 at one year and 1.23 at 2 years) (Stack 2003). In a prospective study of 2195 incident dialysis patients, 33% were referred late (<4 months). Late referral was associated with higher risk of death at one year after initiation of dialysis compared with early referred patients (Kazmi et al., 2004).

Patients who are referred late to nephrology care are reportedly to be those who are older, sicker and with more comorbid disease. In 2007 the UKRR reported that patients who were referred late were significantly older than referred earlier (median age 67.7 vs. 64.8 years) and they had more comorbidity compared to those referred earlier (Ansell et al., 2007). Khan and colleagues (1994) showed that increasing age

and coexisting illnesses are more frequent in patients referred late. Also late referred patients were observed to be unable to ambulate independently and to be unemployed due to disability compared to patients who were referred early (Kazmi et al., 2004).

In dialysis patients randomized control trials have shown different conclusions from observational studies. For example the HEMO study which failed to show any survival advantages of increasing dialysis dose beyond the recommended one, or using high flux dialyzers instead of low flux. Another example is failure of randomized controlled trials to show any benefits from normalisation of haemoglobin values in dialysis patients. Despite the strong suggestion from observational studies about late referral and increased mortality. It is possible that early referral would not lead to predicted reduction in mortality, it would be difficult to design a randomized controlled trial to evaluate whether the referral time effect on survival of dialysis patients was due to confounding or causation.

7.3.4. Vascular Access

Out of patients who started RRT in 2003 and 2004, 49% started with definitive access. Of patients who started on haemodialysis, 41% commenced with definitive access. The UKRR (2006) reported that 51% of all patients started with definitive access. However, only 37% of haemodialysis patients started with permanent access (Ansell et al., 2006)

The analysis in chapters 5 and 6 demonstrated a significantly increased risk of death in patients who received treatment via temporary access. The risk of death was 3 times higher in patients who started dialysis with temporary access compared with those who started with permanent access. Similarly Polkinghorne and colleagues (2004) tested the effect of access type on total mortality in 3749 incident haemodialysis patients from ANZDATA Registry who commenced treatment from 1999 until 2002 and found that use of temporary access in incident haemodialysis patients was associated with significant rise in total mortality. Interestingly, Allon and associates (2006) found that changing the vascular access affected the risk of

death in haemodialysis patients. Change from a catheter to AV access was associated with a substantial decrease in mortality risk. The relative risks for mortality were 3.4 in patients who dialyzed with a catheter; 2.3 in patients switching from an AV access to a catheter, and 1.3 in patients switching from a catheter to an AV access (Allon et al., 2006).

The increased risk of death among individuals who are dialyzed through temporary access could be explained by: -

First, Temporary access is associated with more frequent infection than permanent access, and infection is associated with higher hospitalisation and mortality rates (Churchill et al., 1992 and DOQI 1997d). A study of 7497 prevalent haemodialysis patients from 279 haemodialysis treatment facilities showed that venous catheters were associated with an increased risk of all-cause and infection-related mortality. Patient characteristics independently associated with the presence of a catheter included lower serum albumin, more severely impaired functional status, lower mean URR (63%) compared to those dialyzed with fistula (69.5%) and lower mean blood flow rate during dialysis (328.6 ml/min) compared to those dialyzed with a fistula (418 ml/min) (Pastan et al., 2002). In 2005 the UKRR reported there was evidence of an association between the use of venous catheters and morbidity judged by hospitalisation and staphylococcus aureus infection (Ansell et al. 2005).

Second, venous catheters are associated with inadequate dialysis dose received in haemodialysis patients. In 1996 the USRDS reported that the mean delivered dose Kt/V for patients who started haemodialysis was 1.04 in those dialyzed via a venous catheter and 1.14 in those dialyzed via AV fistula (USRDS 1996). An observational study analyzed data from the USRDS on 5507 prevalent haemodialysis patients. It found that venous catheters are correlated with increased mortality risk when compared with permanent access. Dialysis dose measure by a single pool Kt/V was about 10% lower for patients with venous catheter than those with AV access (Dhingra et al., 2001). The inadequate dialysis dose could be a consequence of lower blood flow defined by DOQI guidelines as less than 300 ml/min (DOQI, 2001b). Pastan and colleagues (2002) found that venous catheters were associated with lower

blood flow compared to AV access. The interrelation of venous catheter, reduced blood flow and inadequate dialysis dose may play a role to increased mortality in patients dialyzed via temporary access The relationship between mortality risk and dialysis adequacy was discussed in chapter 1.

Third, the characteristics of those haemodialysis patients who were dialyzed through venous catheter are different. They are older, sicker and have more frequent comorbid conditions (congestive cardiac failure, ischaemic heart disease, peripheral vascular disease, vascular disease, diabetes, and malignancy) that contribute to increase the risk of mortality in those patients (Dhingra et al., 2001; and Di Iorio et al., 2004).

Vascular access remains a key component for treatment of patients receiving haemodialysis. International differences in outcomes for patient outcomes have been suggested to be associated with vascular access type (Ansell et al., 2006).

7.3.5. CRP

Previous studies have reported that elevated CRP level has been shown to be strongly predictive of an increased risk of future myocardial infarction and predicts mortality in apparently healthy people as well as in patients with established coronary heart disease (Ridker et al., 1998; and Morrow et al., 1998; and Danesh et al., 2004). Higher CRP levels were also found in dialysis patients (Zimmermann et al., 1999; and Ortega et al., 2002). The analysis of chapters 4, 5 and 6 showed that CRP was associated with mortality in both incident and prevalent dialysis patients. Similarly, many observational studies reported that CRP is a significant predictor of death in dialysis patients (Iseki et al., 1999; Yeun et al., 2000; Kato et al., 2001; Wanner et al., 2002).

The high mortality with increased CRP could be explained by atherosclerotic cardiovascular disease being associated with inflammatory disorders. Inflammation evidenced by high levels of CRP is closely related to high levels of atherogenic vascular risk factors and cardiovascular death. Zoccali and colleagues (2000) suggested that the association between inflammation and atherosclerosis is strong in

dialysis patients and they have shown that CRP is independently associated with intima media thickness and the number of atherosclerotic plaques in carotid arteries of dialysis patients. Stenvinkel and collaborates (1999) showed a strong relationship between elevated CRP levels and the thickness of intima media in predialysis patients. Zimmermann and associates (1999) found that patients with elevated CRP levels had significantly higher serum lipoprotein (a), higher plasma fibrinogen and lower levels of HDL and serum albumin which is associated with increased overall mortality and cardiovascular mortality.

On the other hand, recent experimental work claimed that CRP could be a direct cause of death. Pepys and colleagues (2006) showed that therapeutic inhibition of CRP is a promising new approach to cardio-protection. Administration of CRP binding inhibitor [1,6-bis(phosphocholine)-hexane] to rats undergoing acute myocardial infarction stopped the increase in infarct size and cardiac dysfunction produced by injection of human CRP (Pepys et al., 2006).

7.3.6. Serum Albumin

Low albumin levels are powerful predictors of cardiovascular and all cause mortality in haemodialysis patients (Lowrie et al., 1990; and Churchill et al., 1992). The serum albumin concentration in dialysis patients changes with nutritional status and inflammation through their effects on albumin synthesis and increased fractional catabolic rate (Kaysen 2002).

Serum albumin as significant predictor of mortality was found in all univariate analyses, but in multivariate analysis only in chapter 5 (when all comorbid conditions were entered into the analysis instead of using single comorbid score) and chapter 6. Each additional 1 g/l in averaged attained albumin decreased the odds of death in the first two years of treatment by 4%. The association between serum albumin and poor prognosis is widely reported. The Canadian haemodialysis morbidity study showed that patients with a low serum albumin level (≤30g/l) at the start of haemodialysis treatment had a higher probability of hospitalisation and infection related mortality than did patients with higher serum albumin levels (Churchill et al., 1992). The DOPPS study showed a highly significant association between low serum albumin

levels and higher risk of death (Pifer et al., 2002). Also the CANUSA study (1996) showed that low serum albumin levels were associated with an increased risk of hospitalisation and mortality. Foley and colleagues (1996c) found hypoalbuminaemia to be a major adverse prognostic factor in dialysis patients. Kaysen and co-workers (2002) also showed a strong association between serum albumin and mortality in haemodialysis patients.

7.3.7. Serum Cholesterol

In chapter 5 and 6 higher rather than lower serum cholesterol levels at the start of dialysis provided significant survival advantages in patients started RRT in 2003 and 2004. Many prospective studies of dialysis patients have shown the same association of elevated cholesterol levels with lower mortality. In a study of more than 12000 haemodialysis patients; Lowrie and Lew (1990) noted that mortality risk was significantly lower at higher total cholesterol levels. Also Iseki and colleagues (2002) enrolled 1167 chronic haemodialysis patients in a prospective study and showed that low serum cholesterol level was an independent predictor of death in patients on chronic haemodialysis and 5 years survival rates of patients who had high serum cholesterol (>220 mg/dl [5.2 mmol/l]) were better than patients with lower serum cholesterol (<140 mg/dl [3.3 mmol/l]). The high serum cholesterol and lower mortality association is opposite to studies and clinical trials in the general population as discussed in chapter 1.

The inverse association of reduced mortality with high levels of serum cholesterol could be explained by;

First, it is likely to be due to inflammation and malnutrition, not to a protective effect of high serum cholesterol. However, the mechanism by which systemic inflammation and malnutrition may confound the association between cholesterol and mortality is not entirely clear. A Prospective study of 823 haemodialysis patients by Liu and colleagues (2004) used a stratification based on serum albumin, interleukin-6 and CRP levels to evaluate patients with different nutritional and inflammatory status separately. They found that low levels of serum cholesterol were associated with increased mortality in patients with chronic inflammation, but in the absence of

inflammation an elevated level of serum cholesterol was associated with increased mortality, as in the general population.

Second, high cholesterol levels protect against infections, while low cholesterol levels predispose to infections. The lipoprotein pool may serve as an effective scavenger to bind with and neutralize the circulating lipopolysaccharides (bacterial endotoxin) (Ravnskov 2003; Rauchhaus et al., 2000; and Niebauer et al., 1999). Low levels of serum lipoproteins including cholesterol is common in dialysis patients so it has been suggested that elevated levels of serum cholesterol provides a protective effect from bacterial infection as an inhibitor of endotoxin (Kalantar-Zadeh et al., 2004b; and Ravnskov 2004).

Third, presence of comorbid conditions can be associated with low cholesterol levels and increased mortality (Neaton et al., 1992). Study by Iribarren and colleague (1995) demonstrated that the presence of malignancy, liver disease, and other chronic illnesses partially explains the inverse association of low cholesterol level and high mortality.

7.3.8. Subjective Global Assessment (SGA) of nutritional status

Malnutrition is a common risk factor in dialysis patients and associated with increased mortality (Hakim et al., 1993; Owen et al., 1993; Cianciaruso et al. 1995; and CANUSA, 1996). The DOQI guidelines stress the significance of assessment of nutritional status in dialysis patients (DOQI, 1997b). Methods to assess nutritional status in dialysis patients range from simple anthropometric measurements to complex tools (Nelson et al., 1990; Chertow et al., 1995). SGA was originally developed to assess nutritional status in hospitalised post operative patients (Detsky et al., 1987), but has been used in non kidney and kidney patients (Enia et al., 1993; Kalantar-Zadeh et al., 1998).

SGA scoring can effectively discriminate malnourished dialysis patients from those with normal nutrition (Cooper et al., 2002). More importantly, SGA has been shown

to be a dependable predictor of poor outcome in dialysis patients (CANUSA 1996; Chung et al., 2000; Pifer et al., 2002; and Hung et al., 2005).

The results in chapter 4 showed SGA was an independent nutritional factor that predicted the overall mortality of prevalent dialysis patients at 2 years. The risk of death was 2.4 and 5.1 times higher in moderately and severely malnourished patients respectively, compared with the well nourished group. Similarly, The CANUSA study of 680 peritoneal dialysis patients in 14 centers in Canada and the United States showed the value of SGA in predicting survival. The SGA in the CANUSA study was determined by the same method used in chapter 4. The CANUSA study reported that 4.2% were severely malnourished, 51.2% had mild to moderate malnutrition, and 44.6% were well nourished. In the study in chapter 4 severe, mild to moderate and well nourished comprised 3.3%, 33.6% and 63.1% respectively. One reason behind the increase in the proportion of well nourished patients in the study in chapter 4 was because it included prevalent dialysis patients whereas the CANUSA study included incident patients. However, patients included in chapter 4 were representative to the real sample of dialysis population as it involved both haemodialysis and peritoneal dialysis while CANUSA included only peritoneal dialysis. The results of CANUSA study showed a 1 unit change in the SGA total score was associated with 25% difference in the relative risk of death. In chapter 4 the SGA due to small sample size the mortality risk was tested using the well nourished group as a reference. Mortality risk was more than 2 and 5 times higher in moderate malnourished and severe malnourished respectively (CANUSA 1996).

Further support for the significance of using SGA in predicting survival of dialysis patients came from the DOOPS study of 7719 haemodialysis patients. DOPPS study used modified SGA (SGA method used in chapter 4 plus also points for energy level and disease burden) to classify patients into one of 3 modified SGA groups: normally, moderately or severely malnourished. This study showed that several readily measurable nutritional indicators (serum albumin, serum creatinine and BMI) together with SGA were significant predictors of mortality. The mortality risk was increased by 33% and 5% in patients with severe and moderate malnutrition

respectively than patients with normal modified SGA scores (Pifer et al., 2002). However, the DOPPS study included only haemodialysis patients, and the inclusion of patient reports about energy level and disease burden in the score raises questions as to how accurate this modified SGA score is to assess the nutritional status compared with the traditional SGA score. Unlike the DOPPS study out of all nutritional markers entered in the analysis in chapter 4 only SGA was a significant independent predictor of survival.

Although several interventions are available in treatment of malnutrition in haemodialysis patients (e.g. dietary intake intervention, intradialytic parenteral nutrition, nandrolone treatment), they are often of limited efficacy and not without compliance problems and adverse effects. Recently, a multi national randomized control trial conducted at 23 centers in 9 countries aimed to establish clinical proof of the concept that human growth hormone treatment could improve of nutritional status. This study, which included 139 maintenance haemodialysis patients who had serum albumin levels ≤40 g/l, randomly assigned patients to 6 months of treatment with placebo or 20, 35, or 50 μg/kg/per day human growth hormone. The study showed that human growth hormone safely increases lean body mass, serum albumin, serum HDL, and serum transferrin, reduces homocysteine and improves health related quality of life in adult patients who are on maintenance haemodialysis (Feldt-Rasmussen et al., 2007).

Practically, a randomized control study to evaluate the available nutritional markers in predicting nutritional status and survival in dialysis patients will be the key to find a standard method to assess the nutritional status of dialysis patients, especially when some of the used nutritional indicators such as serum albumin, cholesterol and body mass index has been shown inversely associated with survival in dialysis patients.

7.3.9. Congestive Cardiac Failure

Congestive cardiac failure is the most difficult comorbid disease to assess in dialysis patients. Echocardiography remains the gold standard method to assess congestive cardiac failure. In this study the Scottish Renal Registry (SRR) comorbidity criteria (appendix 5) were applied by one observer to assess congestive cardiac failure. The analysis showed 38.3% and 14.8% of incident and prevalent dialysis patients respectively, had congestive cardiac failure. In 2007, USRDS reported the percentage of congestive heart failure in new dialysis patients increased from 30.6% in 1995 to 34.2% in 2006.

Cardiovascular disease is the most common cause of death in dialysis patients. Congestive cardiac failure is a common presenting symptom of cardiovascular disease in the dialysis population and is associated with systolic failure, left ventricular hypertrophy and ischaemic heart disease (Parfrey et al., 1988). Moreover, haemodialysis patients are known to have both a high prevalence and a high risk for developing congestive cardiac failure (Foley et al., 2000; and USRDS 2002). Presence of congestive cardiac failure at the beginning of RRT is a poor prognostic indicator of mortality (Hutchinson et al., 1982).

Congestive cardiac failure was a strong predictor of mortality in the incident patients who started their RRT in 2003 and 2004. In a prospective multicenter cohort study which included 423 dialysis patients by Harnett and colleagues (1995) followed for a mean of 41 months, the median survival of subjects with congestive cardiac failure at baseline was 36 months compared to 62 months in subjects without congestive cardiac failure. They also found that older age, hypertension, diabetes and ischaemic heart disease were independent predictors for the presence of congestive heart failure on initiation of RRT. Ischaemic heart failure, anaemia, hypoalbuminaemia and hypertension were independent predictors for recurrence of heart failure in dialysis patients (Harnett et al., 1995). The DOPPS study also showed the risk of death was increased with cardiovascular comorbidities (heart failure and coronary artery disease) (Goodkin et al., 2003).

7.4. Hospitalisation

Measurements of hospitalisation in dialysis population are important outcome predictors and provide information about the morbidity and the cost of treatment of dialysis patients. The results in chapters 4, 5 and 6 demonstrated that prolonged duration of hospitalisation was associated with older age, and comorbidity. Likewise, in several observational studies the age was shown to be a significant risk factor for increased hospital admissions as older patients (>60 years) had increased hospitalisation rates (Carlson et al., 1984; and Serkes et al.1990). Rocco and colleagues (1996) included 1572 incident dialysis patients and found that increased age, comorbid condition (ischaemic heart disease, congestive cardiac failure, peripheral vascular disease and diabetes) and low serum albumin were associated with higher rates of hospitalisation. Athienites and colleagues (2000) found that higher burden of comorbid conditions at the onset of treatment was strongly correlated with a higher rate of hospitalisation and was an independent predictor of mortality. Furthermore, several observational studies have demonstrated the strong association between increased hospitalisation rates and the presence of several comorbid illnesses in particular cardiovascular disease, congestive cardiac failure, and diabetes (Murphy et al., 2000; Charytan et al., 1986; Serkes et al., 1990; and Burton et al., 1989).

In our study comorbidity was assessed using Charlson, Khan and Davies comorbid scores and all scores were significantly associated with increased hospitalisation rates. Similar observations were reported in other studies. Chandna and colleagues (1999) retrospective study included 292 dialysis patients and showed that age and comorbidity assessed by Khan score were significant factors influencing hospitalisation. Similarly the Charlson index of comorbidity has previously been shown to be independently associated with length of hospital stay for patients admitted with acute chest pain (Matsui et al., 1996) and after stroke (Monane et al., 1996). Beddhu and collaborators (2002) showed that patients who are older and with greater comorbidity assessed by the Charlson index have a greater risk of hospitalisation and death. Fried and associates (2003) showed that the Charlson comorbidity score was a significant predictor of hospitalisation and mortality.

In chapter 4 SGA low score was associated with increased rates of hospital stay, the rate of hospital admission was 1.9% and 5.3% higher in moderate and severe malnourished groups compared with well nourished group. Similar results have been reported in a prospective cohort study of nutritional markers and dialysis adequacy in 680 peritoneal dialysis in 14 centers in Canada and the United states (CANUSA) which demonstrated that hospitalisation rate and mortality risk were increased with worsened nutrition according to SGA and decreased serum albumin (CANUSA 1996).

Furthermore, with the aid of SGA for estimating nutritional status, the malnutrition inflammation score has been developed. The malnutrition inflammation score consists of SGA with 3 severity levels to assess nutritional state combined with anthropometric and biochemical measurement. Kalantar-Zadeh and colleagues (2004) have examined malnutrition inflammation score utility in predicting outcome in 385 haemodialysis patients and showed that malnutrition inflammation score was a good predictor of hospitalisation and mortality in haemodialysis patients.

Conclusions

- A clear definition for all comorbid conditions in particular congestive cardiac failure is important if studies are to be comparable.

- Measuring SGA provides significant additional information about prognosis beyond the regular use of SGA as a nutritional tool.

- The main factors that influenced prevalent patient survival were comorbidity, nutritional status, age and CRP

- The most important predictors of survival in patients starting RRT in 2003 and 2004 were age, comorbidity, initial access and initial serum cholesterol.

- The major cause of mortality in both incident and prevalent patients was cardiovascular disease, followed by infection.

- Hospitalisation was good predictor of outcome in incident and prevalent dialysis patients. Hospital admission was increased in old, high risk and malnourished patients.

- Two year survival rate was essentially unchanged between 2001 and 2006 cohorts despite accepting older and more high risk patients in the more recent study. Hospitalisation was halved in the recent cohort, the reduction noted occurred across a period of moving to a new hospital and multiple changes in working practices and in patient supervision and audit policies.

Recommendations

The conclusions and observations obtained in this study make it possible to suggest policies and areas for further studies.

- SGA should be assessed for all patients at the time of commencing RRT. In Chapter 4 out of all nutritional parameters only SGA was independently found to be associated with survival.
- A randomized controlled trial is needed to evaluate the long term effect of interventional nutritional methods in dialysis patients, because malnutrition is highly prevalent in dialysis patients and potentially reversible.
- Early referral to nephrology care might help avoid the disadvantages of late referral that have been reported in many observational studies. But the scale of benefit from this may not as high as hoped. Nevertheless it is worth referring patients because of the advantages listed in chapter 7.
- Commencing dialysis with permanent vascular access. The increased mortality associated with temporary access in incident dialysis patients in the Edinburgh Renal Unit suggests that the type of access employed may have subsequent implications for survival that provide an additional reason for aggressive pursuit of starting dialysis with permanent access.
- Adopting a method of recording comorbidity (standardized comorbidity score) uniformly in a straightforward manner and with clear definitions of the co-morbid conditions, in particular congestive cardiac failure, so that survival statistics can be meaningfully compared between patients in different renal units.
- Long term follow up of the 2003 and 2004 cohort to assess the survival of those patients in 5 and 10 years will be valuable.
- Multicenter studies to evaluate factors associated with survival in dialysis patients in Scotland or/and UK will be informative.

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Appendices

Appendix 1: Comorbidity scoring system

Appendix 1.1: Charlson Index

weight	condition
1	Myocardial infarction Congestive cardiac failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate to severe renal failure (excluded in our study) Diabetes with end organ damage Any tumour (solid tumour without metastases diagnosed in past 5 years) Leukaemia (acute and chronic and Polycythemia vera) Lymphoma (includes Hodgekins, Waldenstroms, Myeloma, lymphosarcoma)
3	Moderate or severe liver disease (cirrhosis, portal hypertension, varicies)
6	Metastatic solid tumours HIV

Appendix 1.2: Khan score

Grade-0 (low risk)	Age<70 years and no comorbid disease
Grade-1 (medium risk)	Age 70-80 years, or <70 years age with any one of the following: Angina, previous myocardial infarction, cardiac failure, chronic obstructive airway disease, pulmonary fibrosis, or liver disease (cirrhosis, chronic hepatitis), peripheral vascular and cerebrovascular diseases or <70 with diabetes mellitus
Grade-2 (high risk)	Age>80 years, or <80 years with two or more organ dysfunction, cardiopulmonary disease, visceral malignancy, or 70-80 years with diabetes or cardiopulmonary disease.

Appendix 1.3: Davies score

Conditions
Ischemic heart disease (defined as prior MI, angina, or ischemic changes on ECG)
Congestive cardiac failure
Peripheral vascular disease
Malignancy
Diabetes mellitus
Collagen vascular disease
Other significant pathology (chronic pulmonary diseases)

Appendix 2: ERA-EDTA Primary Renal Diagnosis Codes and Groupings

	Group 1 Primary Glomerulonephritis
10	Glomerulonephritis histologically NOT examined
11	Focal segmental glomerulosclerosis with nephrotic syndrome in children
12	IgA nephropathy (proven by immunofluorescence, not 85)
13	Dense deposit disease, membranoproliferative GN; type II (proven by immunofluorescence and/or electron microscopy)
14	Membranous nephropathy
15	membranoproliferative GN; type I (proven by immunofluorescence and/or electron microscopy – not code 84 or 89)
16	Crescentic (extracapilliary) glomerulonephritis (type 1,II, III)
17	Focal segmental glomerulonephritis with nephrotic syndrome in adults
19	Glomerulonephritis; histologically examined, not given above
	Group 2: Interstitial Nephropathies
20	Pyelonephritis cause not specified
21	Pyelonephritis associated with neurogenic bladder
22	Pyelonephritis due to congenital obstructive uropathy with/without vesico-ureteric reflux
23	Pyelonephritis due to acquired obstructive uropathy
24	Pyelonephritis due to vesico-ureteric reflux without obstruction
25	Pyelonephritis due to urolithiasis
29	Pyelonephritis due to other cause
30	Interstitial nephritis (not pyelonephritis) due to other cause, or unspecified (not mentioned
31	Interstitial nephropathy due to analgesic drugs
32	Interstitial nephropathy due to cis-platinum
33	Interstitial nephropathy due to cyclosporin A
34	Lead induced interstitial nephropathy
39	Drug induced interstitial nephropathy not mentioned above
40	Cystic kidney disease - type unspecified
41	Polycystic kidneys; adult type (dominant)
42	Polycystic kidneys; infantile (recessive)
43	Medullary cystic disease; including nephronophthisis
49	Cystic kidney– disease - other specified type
50	Hereditary/Familial nephropathy - type unspecified
51	Hereditary nephritis with nerve deafness (Alport's Syndrome)
52	Cystinosis
53	Primary oxalosis
54	Fabry's disease
59	Hereditary nephropathy - other specified type
61	Oligomeganephronic hypoplasia
63	Congenital renal dysplasia with/without urinary tract malformation
66	Syndrome of agenesis of abdominal muscles (Prune Belly)
92	Gout nephropathy (urate)
93	Nephrocalcinosis and hypercalcaemic nephropathy

	Group 3: Multisystem Diseases
70	Renal vascular disease - type unspecified
71	Renal vascular disease due to malignant hypertension (No PRD)
72	Renal vascular disease due to hypertension (No PRD)
73	Renal vascular disease due to polyarteritis
74	Wegeners Granulomatosis
75	Ischaemic renal disease / cholesterol embolisation
76	Glomerulonephritis related to liver cirrhosis
78	Cryoglobulinaemic glomerulonephritis
79	Renal vascular disease - due to other cause (not given above and not code 84-88)
82	Myelomatosis/light chain deposit disease
83	Amyloid
84	Lupus erythematosus
85	Henoch-Schonlein purpura
86	Goodpasture's Syndrome
87	Systemic sclerosis (scleroderma)
88	Haemolytic uraemic Syndrome (including Moschcowitz Syndrome)
89	Multi-system disease - other (not mentioned above)
90	Tubular necrosis (irreversible) or cortical necrosis (different from 88)
91	Tuberculosis
94	Balkan nephropathy
95	Kidney tumour
96	Traumatic or surgical loss of kidney
	Group 4: – Diabetes
80	Diabetic glomerulosclerosis or diabetic nephropathy
	Group 5: - Not Known and Other
00	Chronic renal failure; aetiology uncertain/unknown/unavailable
60	Renal hypoplasia (congenital) - type unspecified
99	Other identified renal disorders

Appendix 3: ERA-EDTA Cause of Death Codes

00	Cause of Death uncertain/not determined
11	Myocardial ischaemia and infarction
12	Hyperkalaemia
13	Haemorrhagic pericarditis
14	Other causes of cardiac failure
15	Cardiac arrest, cause unknown
16	Hypertensive cardiac failure
17	Hypokalaemia
18	Fluid overload
21	Pulmonary embolus
22	Cerebrovascular accident
23	Gastro-intestinal haemorrhage
23	Gastro-intestinal haemorrhage
24	Haemorrhage from graft site
25	Haemorrhage from vascular access or dialysis circuit
26	Haemorrhage from rupture vascular aneurysm (not codes 22,23)
27	Haemorrhage from surgery (not codes 23,24,26)
28	Other haemorrhage (not codes 23-27)
29	Mesenteric infarction
29	Mesenteric infarction
31	Pulmonary infection (bacterial)
32	Pulmonary infection (viral)
33	Pulmonary infection (fungal or protozoal)
34	Infections elsewhere (except viral Hep.)
35	Septicaemia
36	Tuberculosis (lung)
37	Tuberculosis (elsewhere)
38	Generalized viral infection
39	Peritonitis (not code 70)
41	due to Hepatitis B virus
42	due to other viral Hepatitis
43	due to drug toxicity
44	Cirrhosis-not viral
45	Cystic liver disease
46	Liver failure-cause unknown
51	Patient refused further treatment
52	Suicide
53	Therapy ceased for any other reason
61	Uraemia caused by graft failure
62	Pancreatitis
62	Pancreatitis
63	Bone marrow depression
64	Cachexia
66	Malignant disease possibly .induced by immunosuppression. therapy
67	Malignant disease except those of 66

69	Dementia
70	Sclerosing (or adhesive) peritoneal disease
70	Sclerosing (or adhesive) peritoneal disease
71	Perforation of peptic ulcer
71	Perforation of peptic ulcer
72	Perforation of colon
72	Perforation of colon
81	Accident related to treatment
82	Accident unrelated to treatment
99	Other cause of death please specify

Appendix 4: Evaluation form for Subjective Global Assessment

Medical History

Weight changes

- □ Usual dry weight: kg
- □ Current dry weight: kg
- □ *(Weight 3 months ago:* *kg ------ %)*
- □ Weight 6 months ago: kg
- □ Overall change in past 6 months: kg------- %

% change over past 6 months:

- □ gain or <5% loss
- □ 5-10% loss
- □ >10% loss

Change in the past 2 weeks:

□ increase □ no change □ decrease

SGA score 1: Weight change						
Severe		Mild	Moderate		Normal	
1	2	3	4	5	6	7

Dietary intake

□ no change:

□ adequate intake □ inadequate intake

□ change:

□ increase □ decrease

Overall duration: -------- weeks

Change in previous 6 months:

□ yes □ no

changes in the past 2 weeks:

□ yes □ no

Gastrointestinal Symptoms

□ anorexia; □ nausea; □ vomiting; □ diarrhoea

Duration: ---- weeks

SGA score 2: Dietary intake & GIT symptoms						
Severe		Mild	Moderate		Normal	
1	2	3	4	5	6	7

Physical Examination

Muscle wasting

□ Biceps □ Triceps

Subcutaneous fat

□ Triceps □ Chest □ Eyes

□ Perioral □ Interosseous □ Palmar

Oedema

□ Hands □ Sacral □ lower extremity

SGA score 3 & 4: : Physical Examination						
Severe		Mild	Moderate		Normal	
1	2	3	4	1	2	3

Overall SGA Classification

severe		moderate	mild		normal	
1	2	3	4	5	6	7
C		**B**			**A**	

Appendix 5: Scottish Renal Registry (SRR) comorbid conditions

Comorbid conditions	
Congestive Cardiac Failure (CCF)	Clinical diagnosis of CCF prior to starting RRT. Echocardiogram Evidence Angiographic Evidence Fluid overload may be difficult to exclude and where reasonable clinical doubt exist CCF should be recorded.
Myocardial Infarction (MI)	Diagnosis of MI at any time prior to date of starting RRT. Based on clinical history and either diagnostic ECG changes or diagnostic biochemical indices.
Peripheral vascular disease	Clinical history of intermittent claudication. Angiographic evidence of peripheral artery atheroma.
Chronic Pulmonary disease	Clinical diagnosis based upon pulmonary function tests or pulmonary imaging
Foot ulcer	Any cause of foot ulceration except venous eczema. Diabetic foot ulcer, ischaemic foot ulcer included.
Malignancy	Skin basal cell carcinoma excluded All solid organ and haematological malignancies included.
Serum albumin at start of RRT	